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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Thrombosis
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

DAPT should be prolonged in patients with acute coronary syndrome ?

João Morais

Head of Cardiology Division
Leiria Hospital Centre
Chairman WG Thrombosis

CENTRO HOSPITALAR LEIRIA

Serviço de Cardiologia
Centro Hospitalar de Leiria

Disclosures related with the current topic

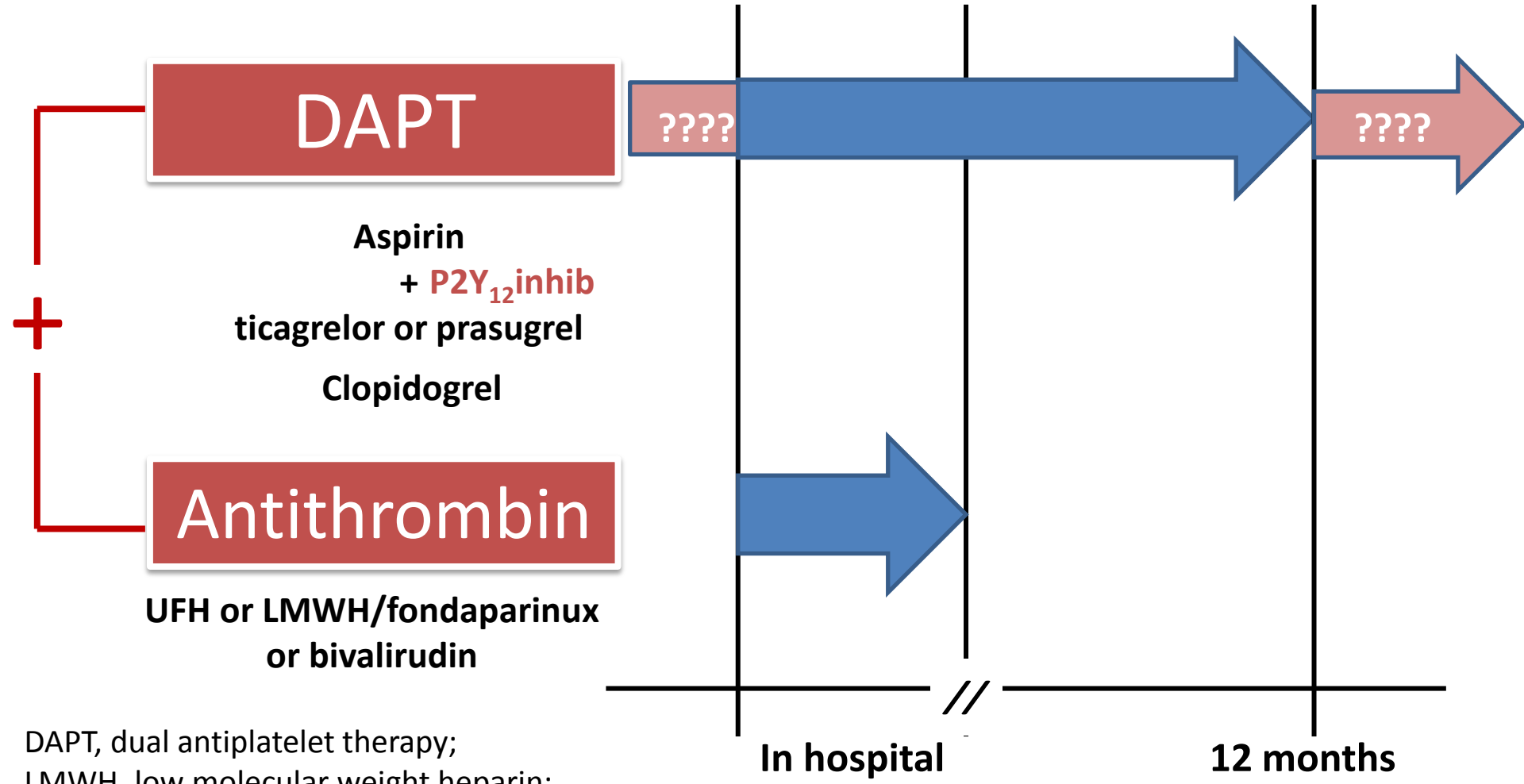
João Morais

<u>Honoraria received from Astra Zeneca and Merck Sharp & Dhome</u>

Consulting activities and invited speaker

National and international levels

Antithrombotic environment in patients with ACS



DAPT, dual antiplatelet therapy;
LMWH, low molecular weight heparin;
UFH, unfractionated heparin

Routine therapies in the acute, subacute and long term phase of STEMI

DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I	C
• 1 month for patients receiving BMS;	I	C
• 6 months for patients receiving DES.	IIb	B

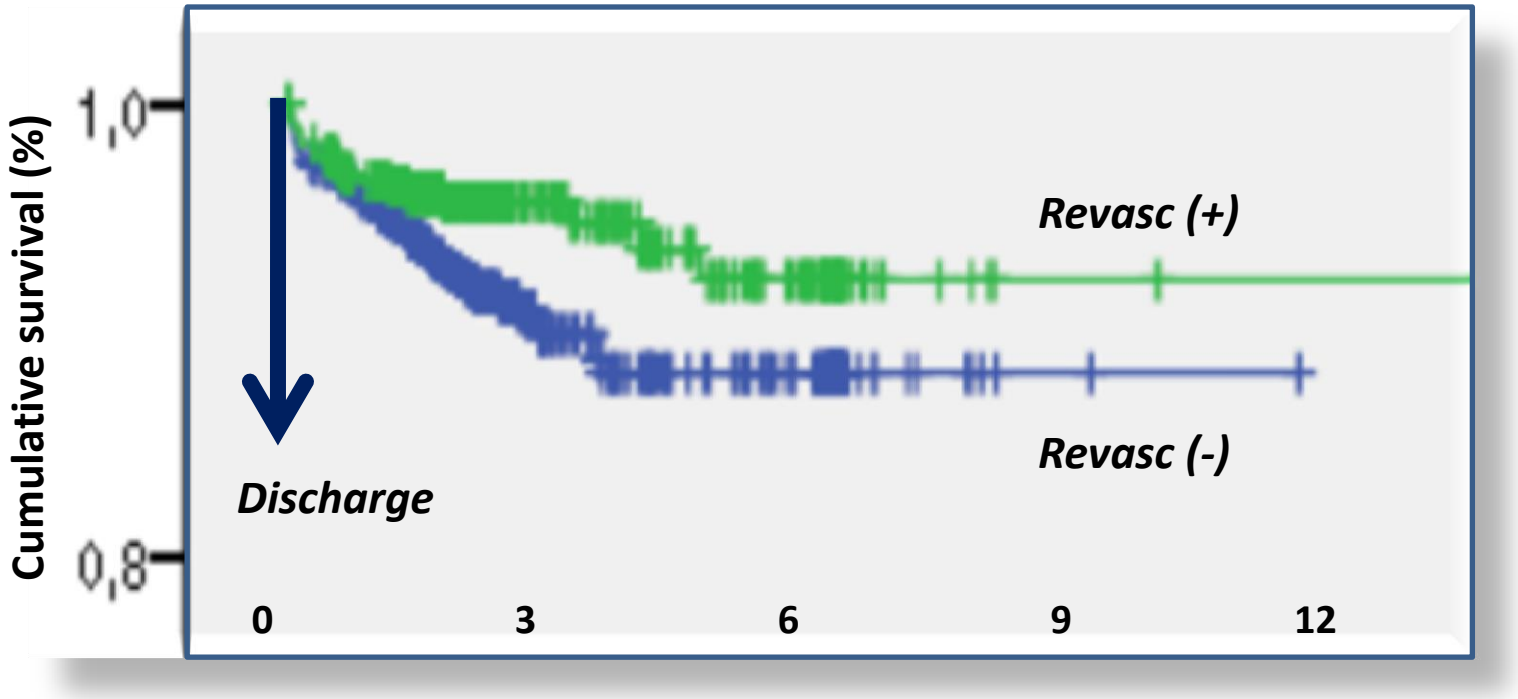
Stent oriented strategy

Patient oriented strategy

DAPT post ACS

Rationale for 12 months of treatment duration

Single centre (n=965)



Total death / AMI at 12 months

Event rate

Revascularization *(+) 5.2%*

Revascularization *(-) 9.0%*

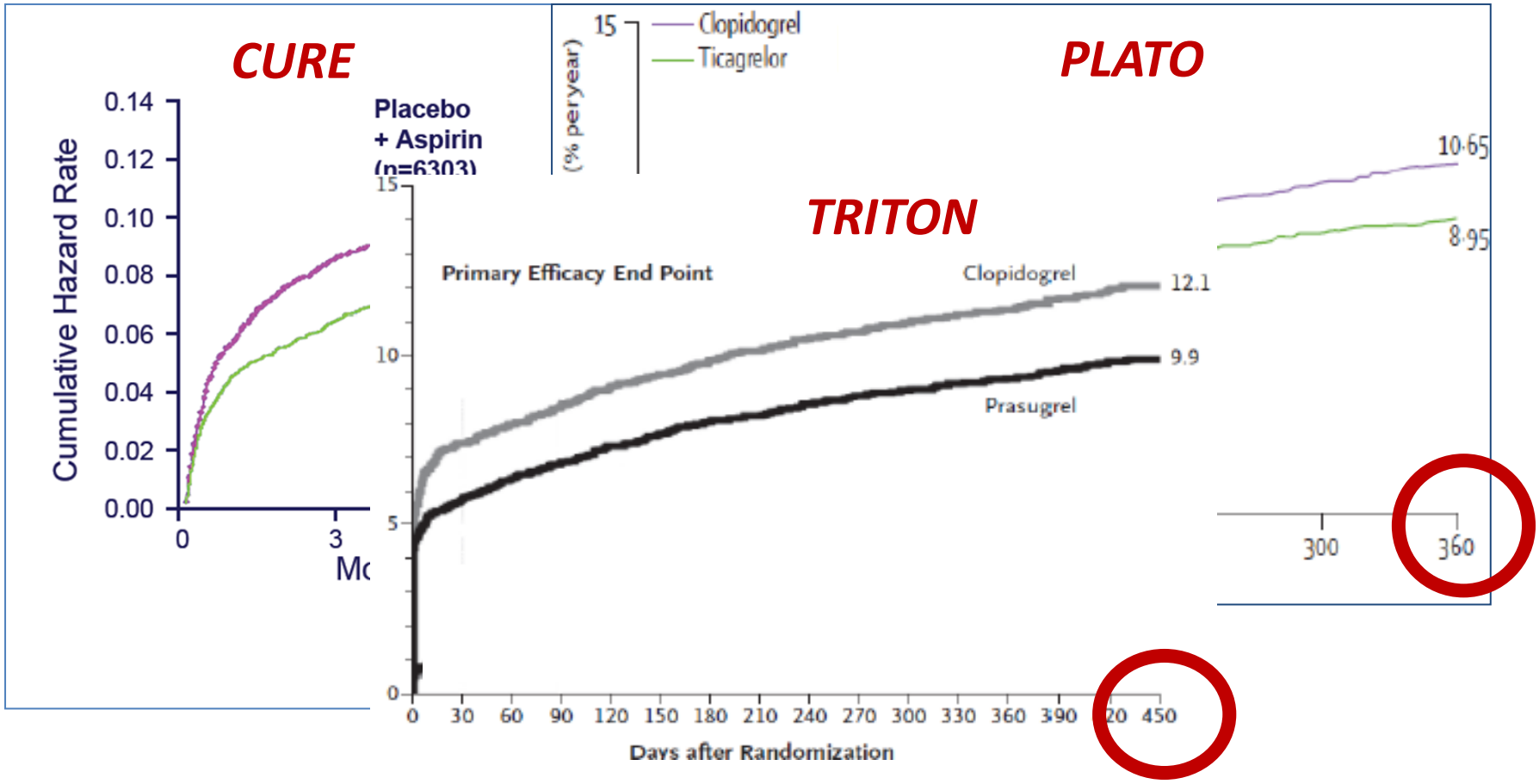
Morais J et al

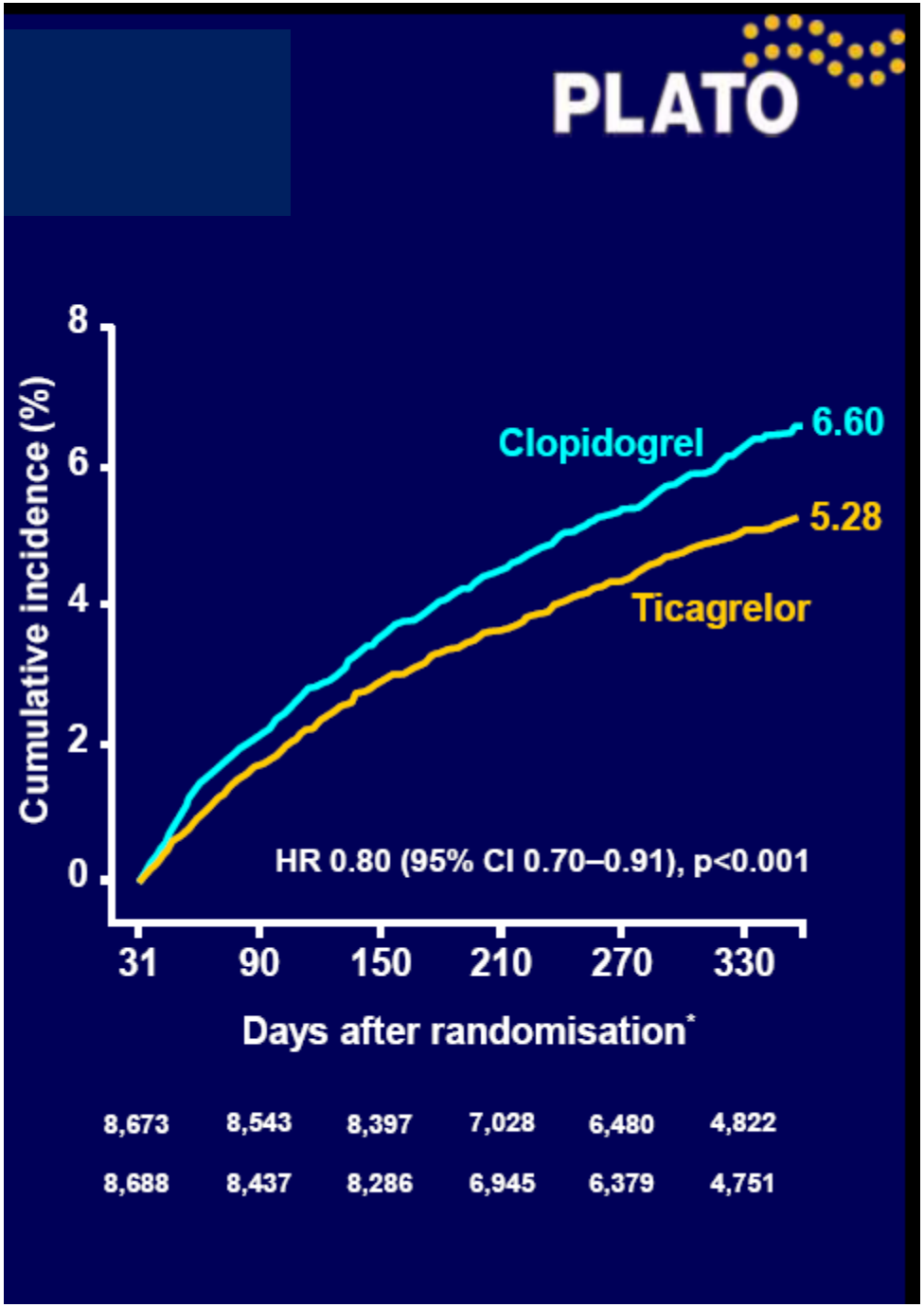
Unpublished data

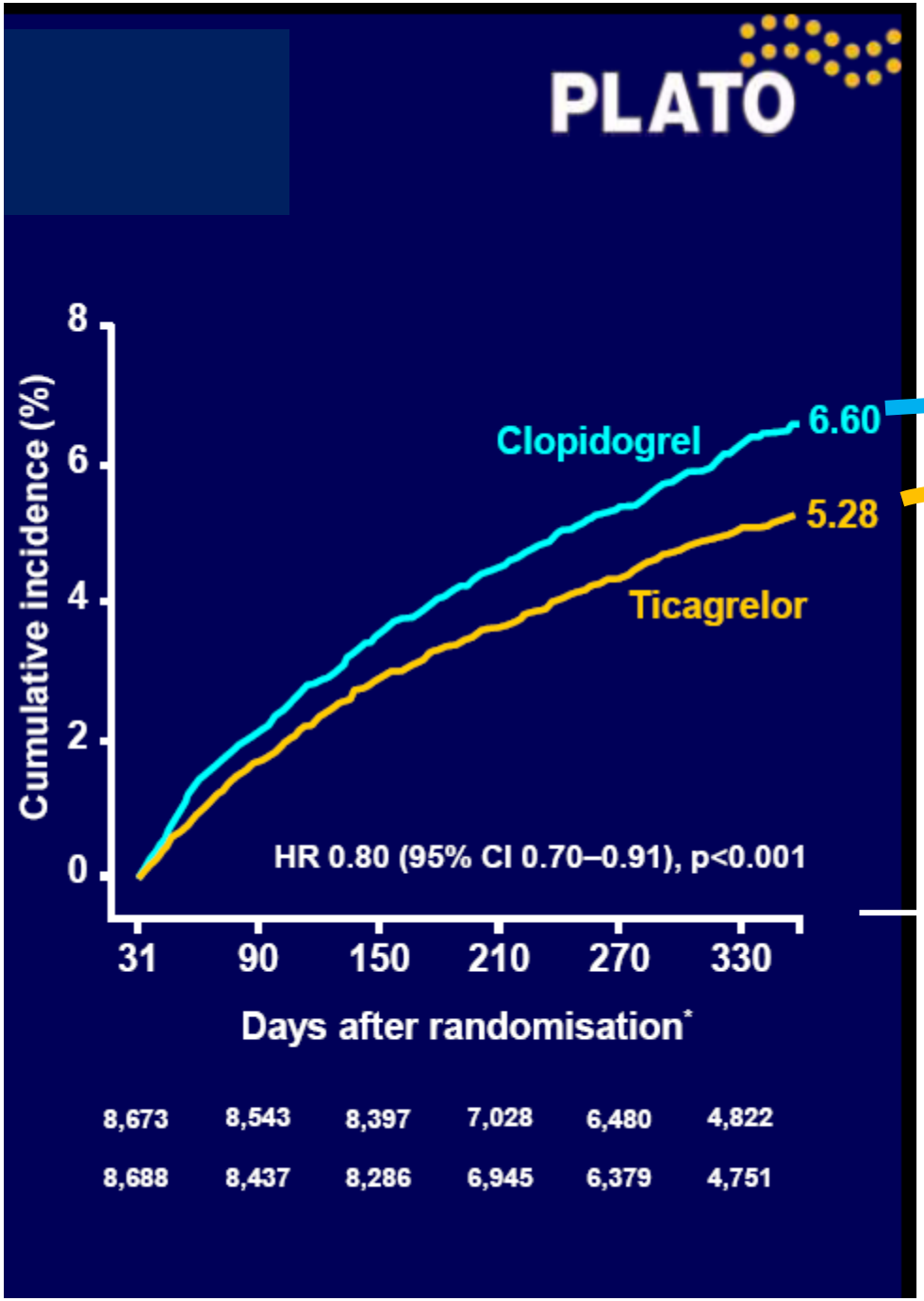
Serviço de Cardiologia
Centro Hospitalar Leiria Pombal

DAPT post ACS

Rationale for 12 months of treatment duration




PLATO
Cumulative incidence (%)
8
6
4
2
0
Clopidogrel
6.60
Ticagrelor
5.28
HR 0.80 (95% CI 0.70–0.91), p<0.001
31
90
150
210
270
330
Days after randomisation*
8,673 8,543 8,397 7,028 6,480 4,822
8,688 8,437 8,286 6,945 6,379 4,751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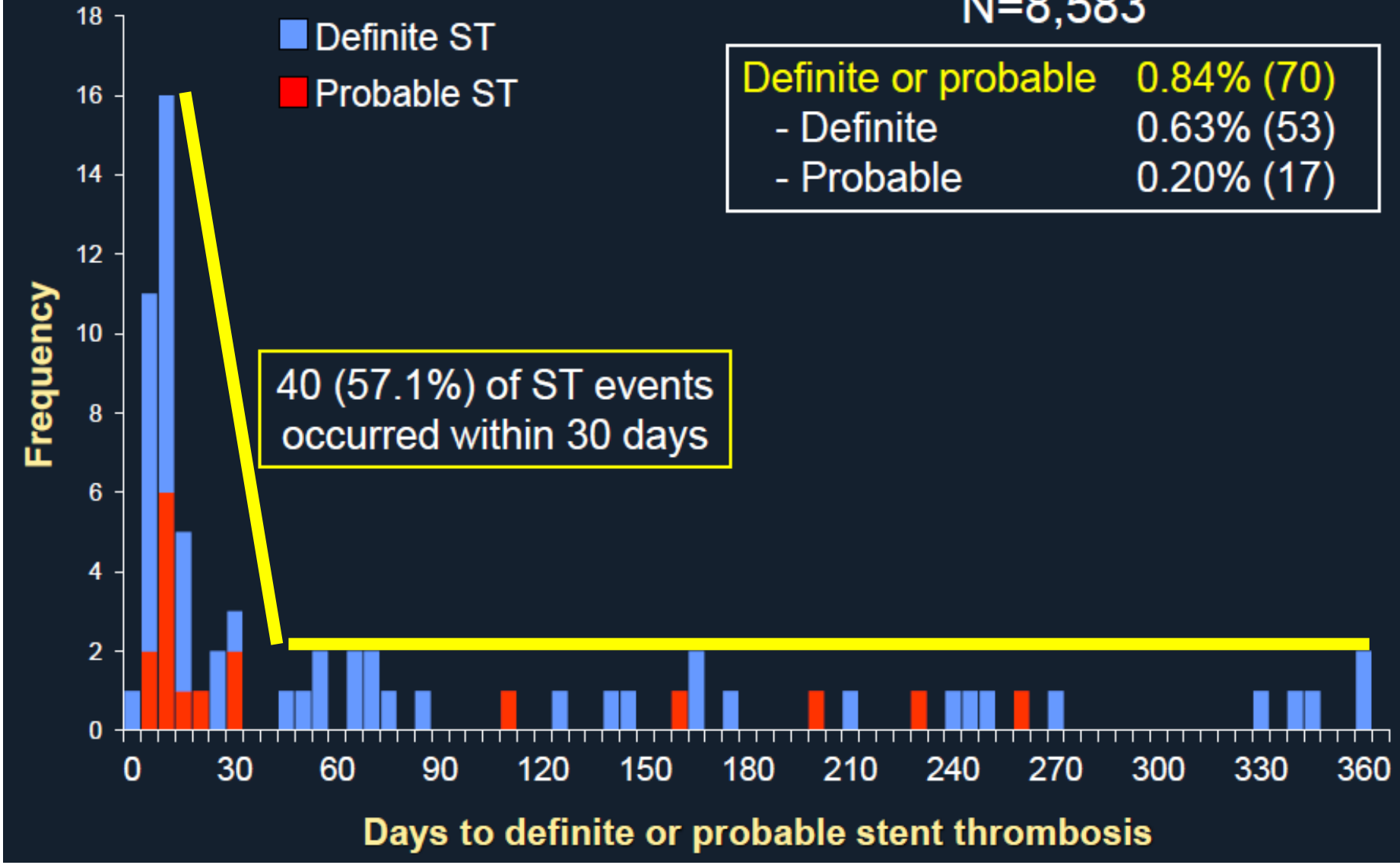
Stent oriented strategy

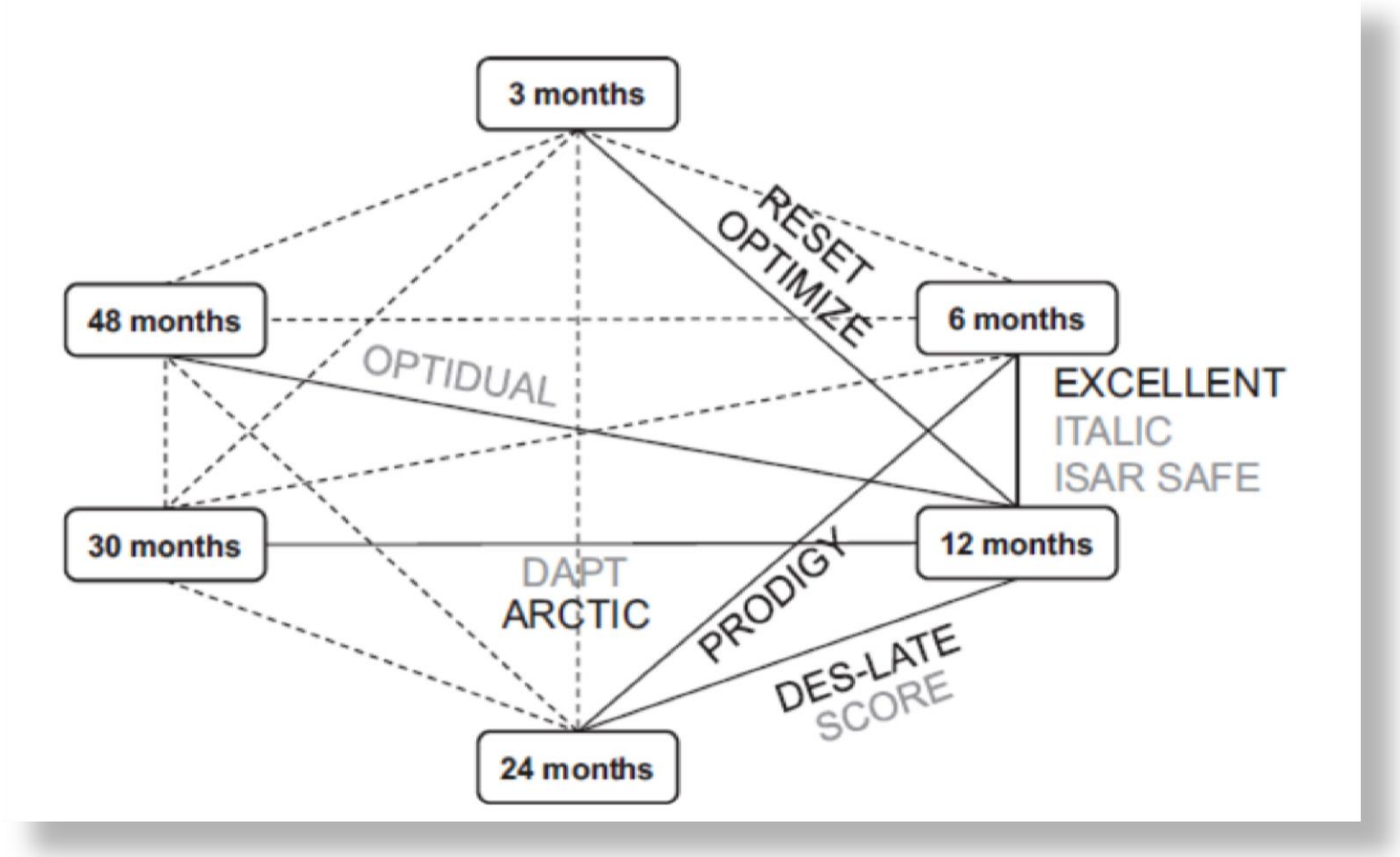
ADAPT-DES: Time to First Stent Thrombosis

70 patients (0.84%) developed 74 ST events (ARC def/prob)



DAPT post stent implantation

Time duration can be shorten ?

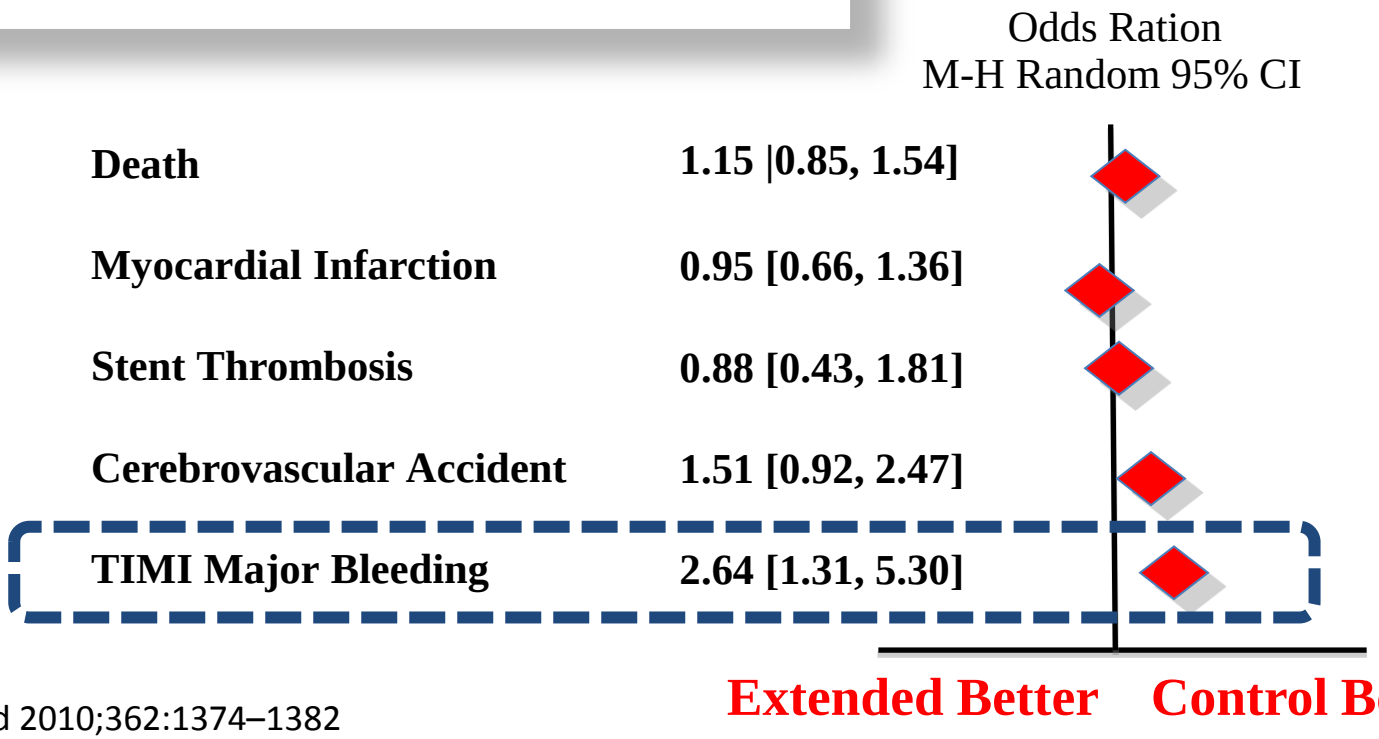


Capodanno D, *Circulation. 2013;128:2785-2798*

Clinical Impact of Extended DAPT after PCI

A metanalysis of Randomized trials (n=8231)

Trial *(Journal)*	Stent types	No. of pts	DAPT duration
EXCELLENT (*Circ 2012*)	SES, EES	1,443	6 vs. 12 months
PRODIGY (*Circ 2012*)	BMS, PES, E-ZES, EES	1,970	6 vs. 24 months
REAL/ZEST LATE (*NEJM 2010*)	SES, PES, E-ZES	2,701	12 vs. 24 months
RESET (*JACC 2012*)	SES, E-ZES, R-ZES, EES	2,148	3 vs. 12 months



N Engl J Med 2010;362:1374–1382
Circulation 2012;125:2015–2026
Circulation 2012;125:505–513.
J Am Coll Cardiol. 2012 Oct 9;60(15):1340-8.

Cassese et al Eur Heart Journal 2012; 33: 3078-3087

DAPT post stent implantation

Stent thrombosis – new generation of stents

49 RCTs, 50 844 pts
ARC definitions

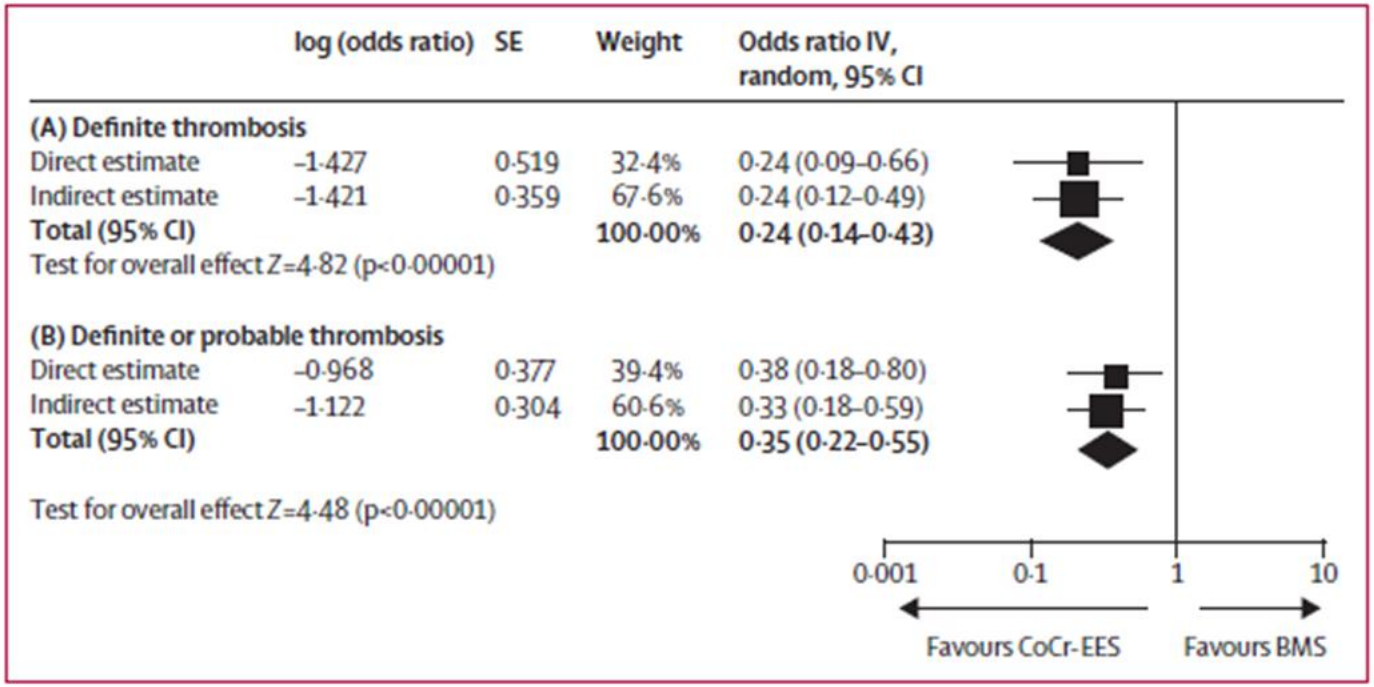


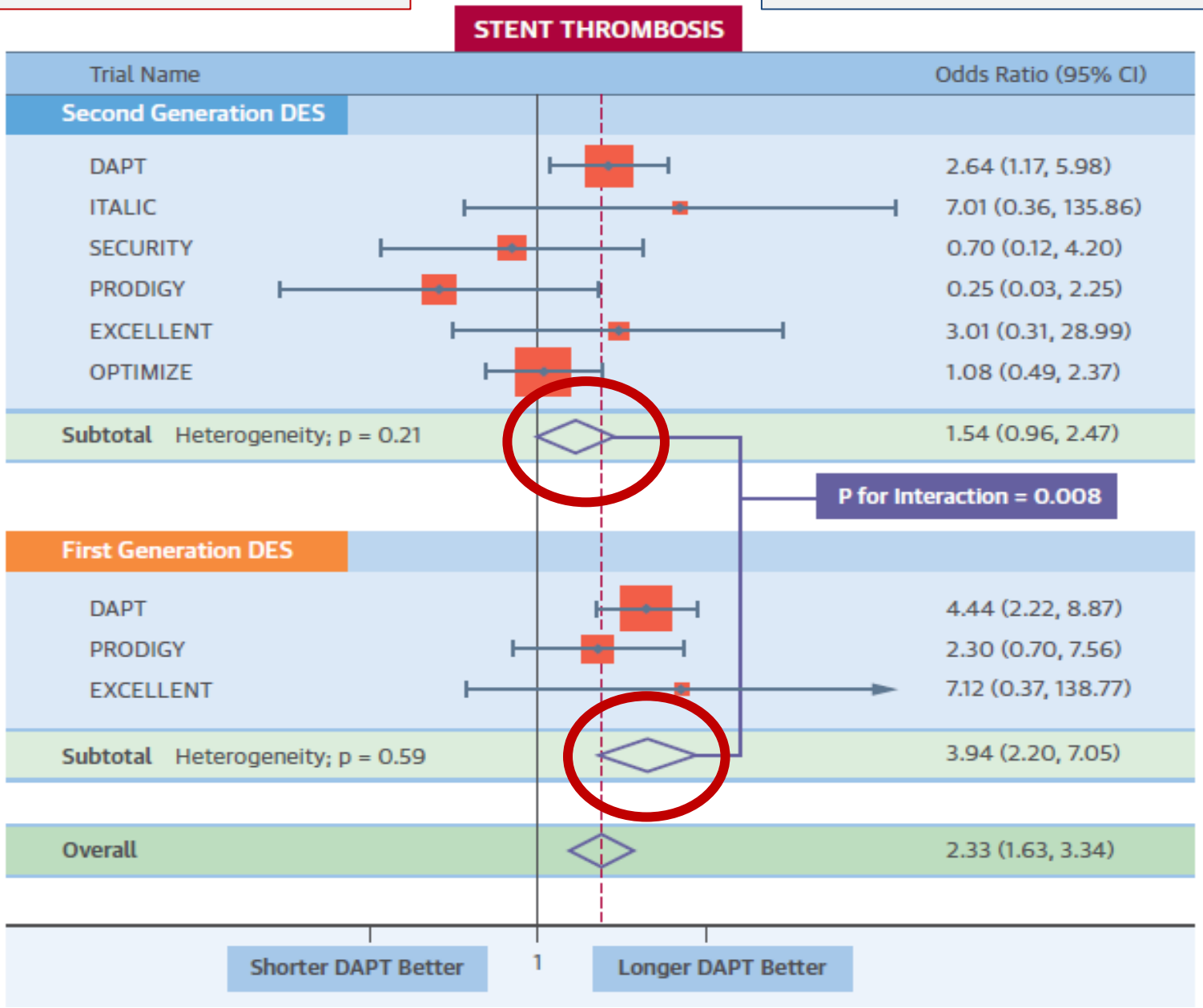
***Figure 5*: Consistency between direct and indirect estimates of definite (A) and definite or probable (B) stent thrombosis at 1 year between CoCr-EES and BMS**

CoCr-EES=cobalt-chromium everolimus-eluting stents. BMS=bare-metal stents. IV=inverse variance. SE=standard error.

Palmeri et al. Lancet 2012;379:1392-1402

Drug eluted stents

1st vs 2nd generation

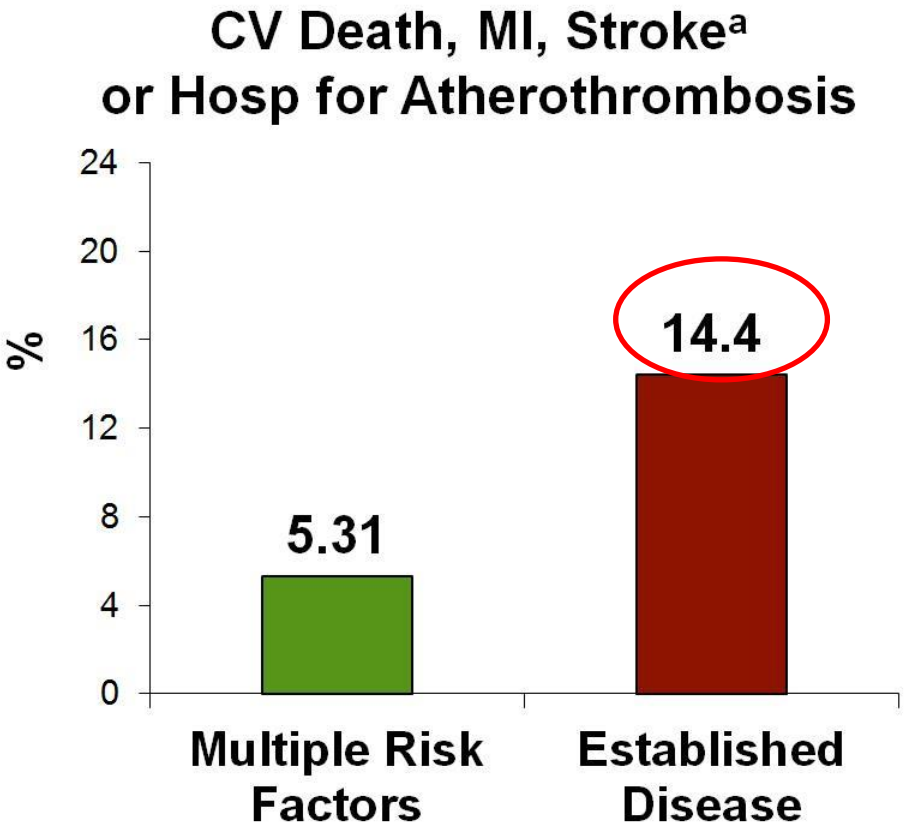


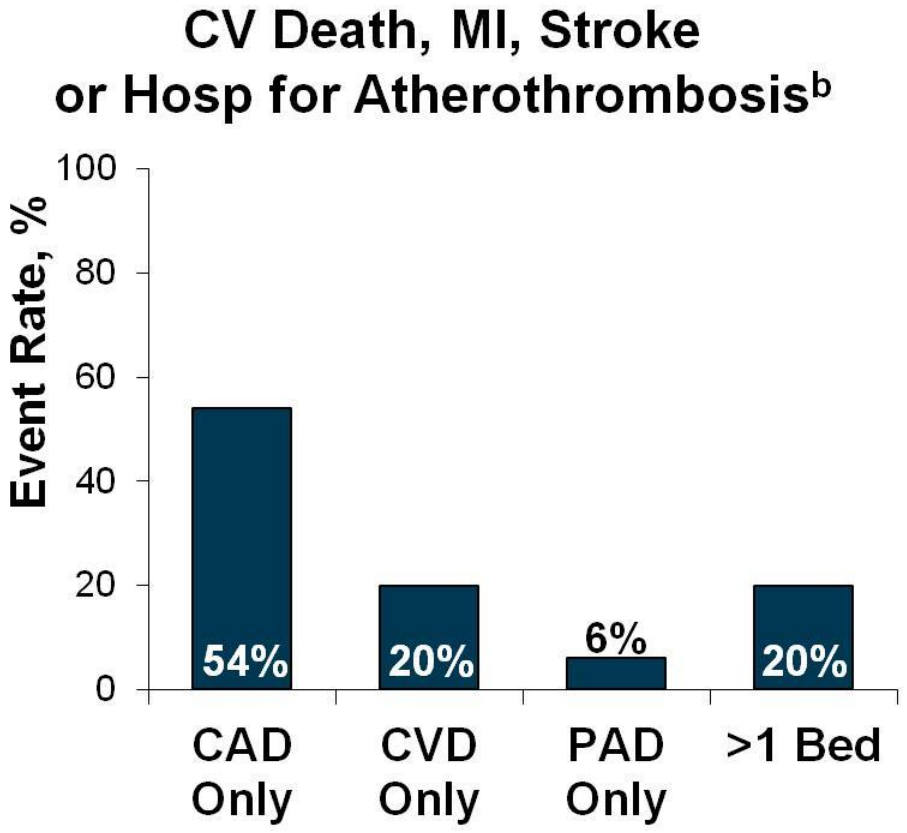
Giustino G, et al. J Am Coll Cardiol 2015;65:1298–310

Patient oriented strategy

Outcomes in patients with atherosclerosis

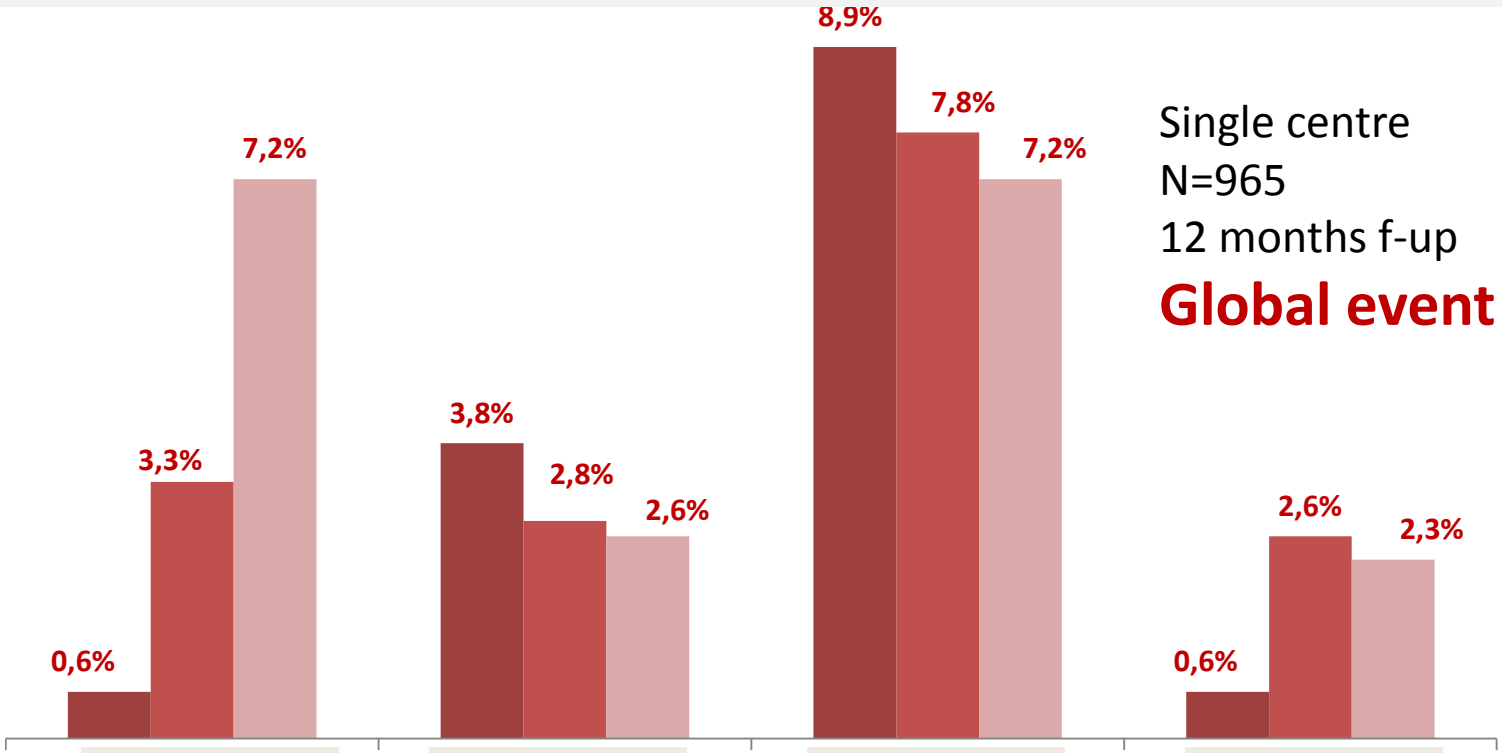
REACH Registry (1-y outcomes) 64,977 pts ≥ 45 years old





a. Steg P, et al. *JAMA*. 2007;297:1197-06[1]; b. Morrow D, et al. *N Engl J Med*. 2012;366:1404-13.[2]

Outcomes in post ACS patients



Single centre
N=965
12 months f-up

Global event rate 14,1%

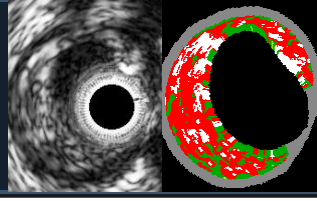
Unstable angina

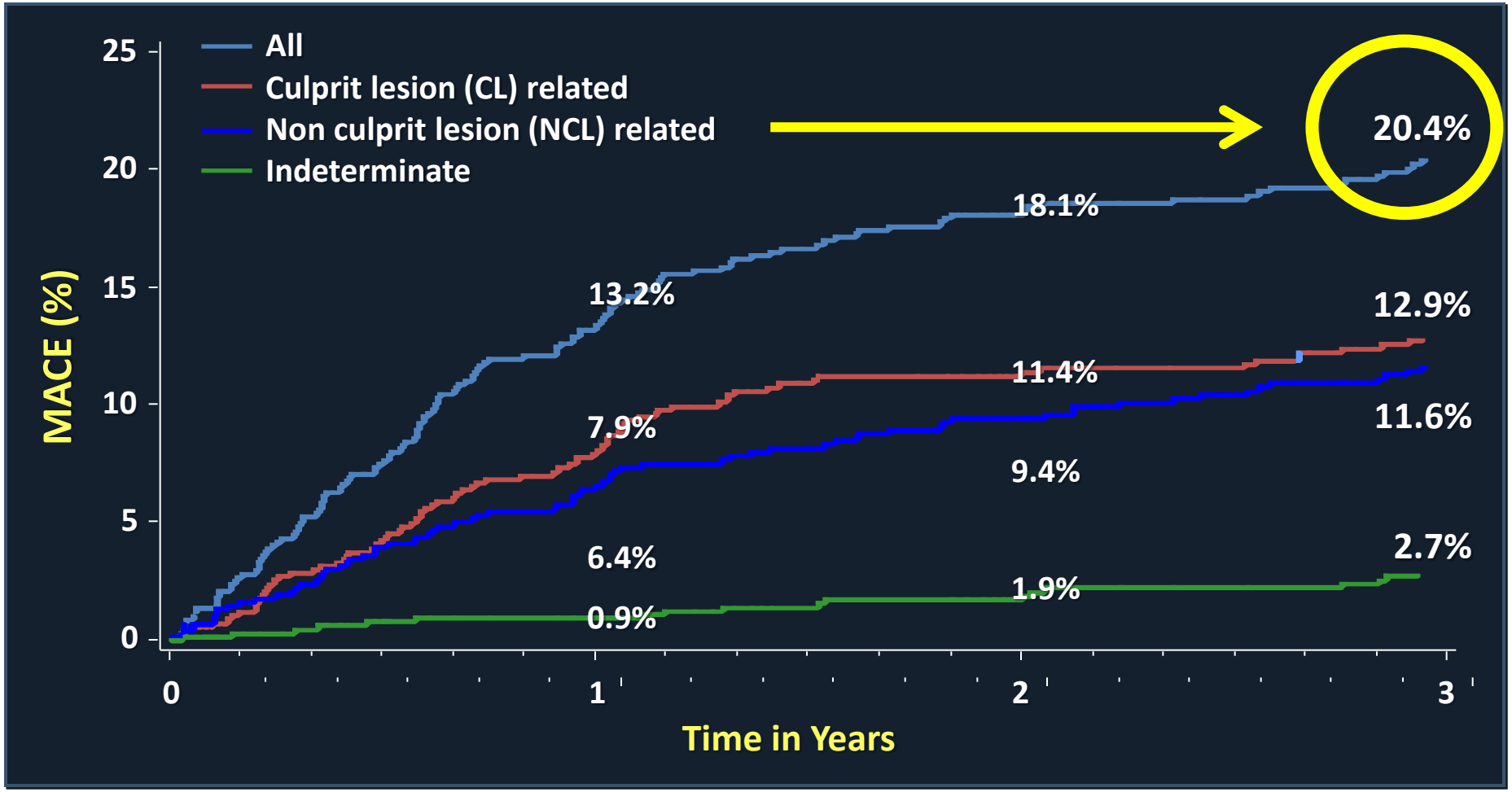
STEMI

NSTEMI

João Morais, 2016 to be published

PROSPECT: MACE



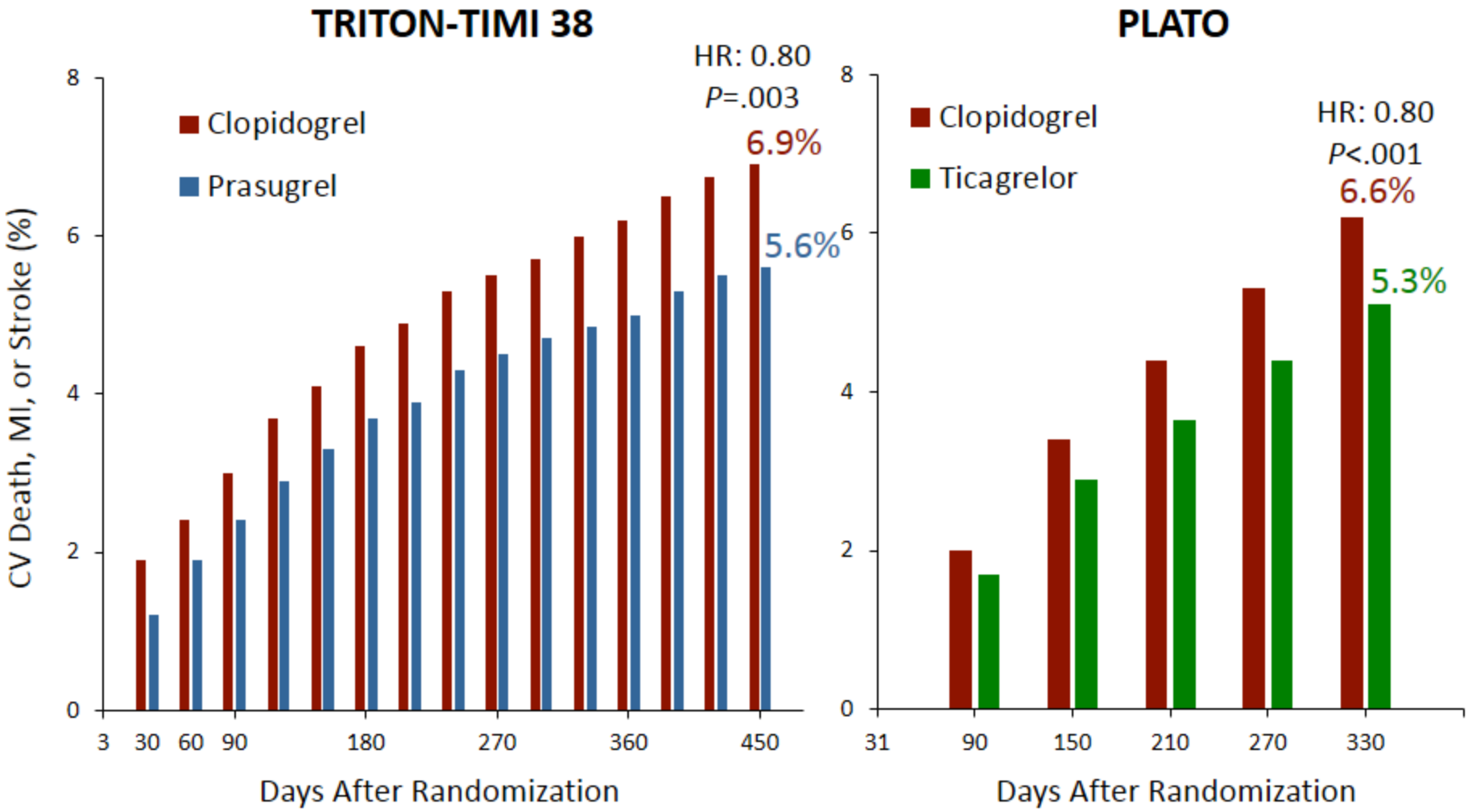


Number at risk

ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

Extended DAPT

Continued Divergence of Event Curves With More Potent Long-term $P2Y_{12}$ Inhibition



Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057.

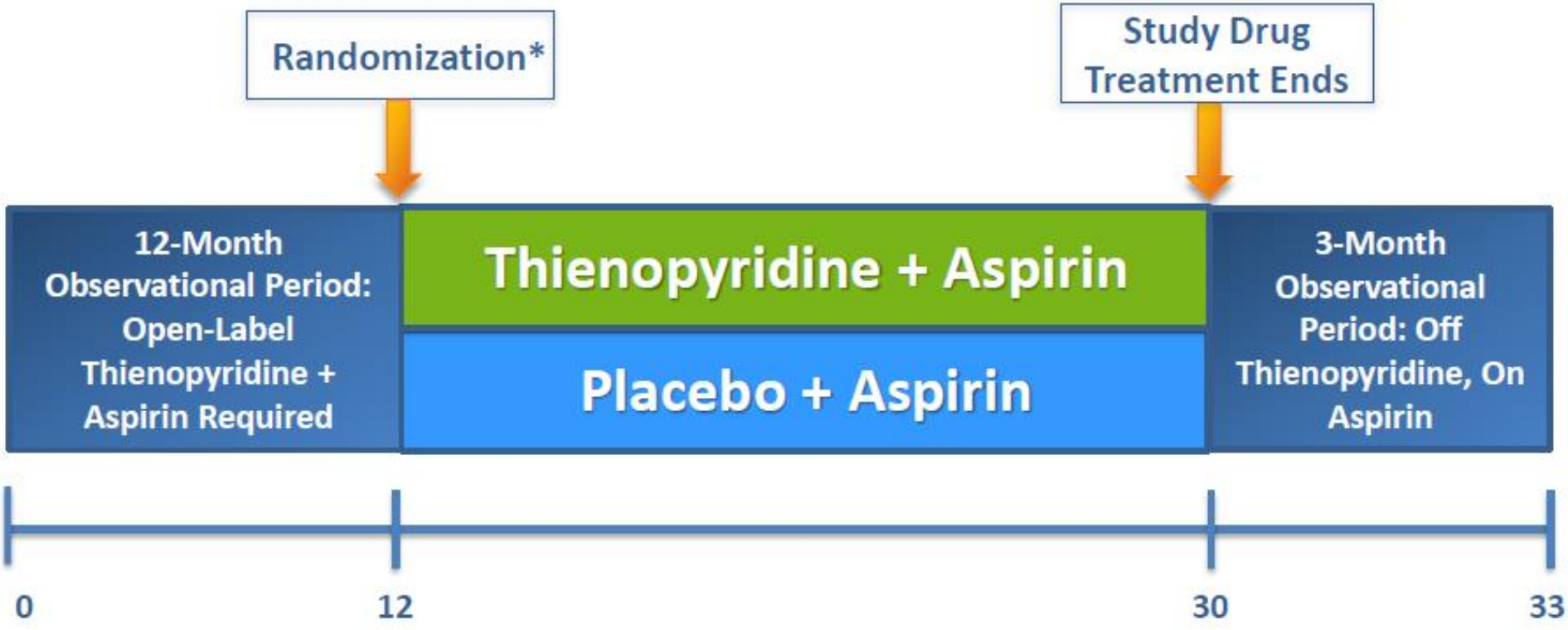
DAPT STUDY

Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures

Laura Mauri, Dean J. Kereiakes, Robert W. Yeh, Priscilla Driscoll-Shempp, Donald E. Cutlip, P. Gabriel Steg, Sharon-Lise T. Normand, Eugene Braunwald, Stephen D. Wiviott, David J. Cohen, David R. Holmes, Mitchell W. Krucoff, James Hermiller, Harold L. Dauerman, Daniel I. Simon, David E. Kandzari, Kirk N. Garratt, David P. Lee, Thomas K. Pow, Peter Ver Lee, Michael J. Rinaldi, and Joseph M. Massaro

on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators

Design



Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

Mauri, Kereiakes et al AHJ 2010; 160(6): 1035-1041

ClinicalTrials.gov number NCT00977938

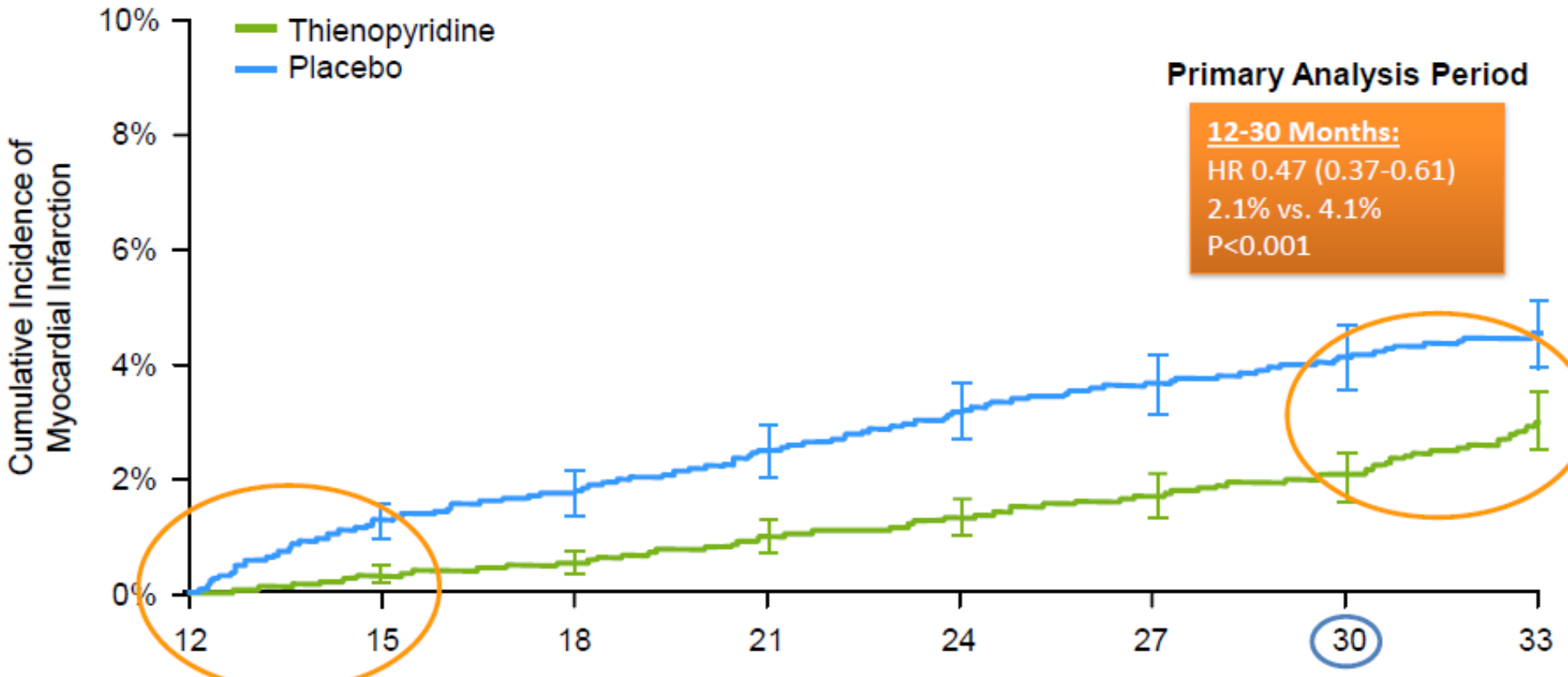
Baseline Demographics

DAPT STUDY

	Thienopyridine N=5020	Placebo N=4941	P-value
Age (years)	61.8	61.6	0.24
Female	24.7%	26.0%	0.15
Race – Non White	8.9%	8.6%	0.67
Ethnicity-Hispanic or Latino	3.2%	3.3%	0.91
Weight – kg	91.5	91.5	0.93
BMI	30.5	30.6	0.92
Diabetes Mellitus	31.1%	30.1%	0.28
Hypertension	75.8%	74.0%	0.03
Cigarette Smoker	24.6%	24.7%	0.91
Prior PCI	30.4%	31.0%	0.50
Prior CABG	11.3%	11.8%	0.49
NSTEMI	15.5%	15.5%	0.93
STEMI	10.6%	10.3%	0.65

Myocardial Infarction

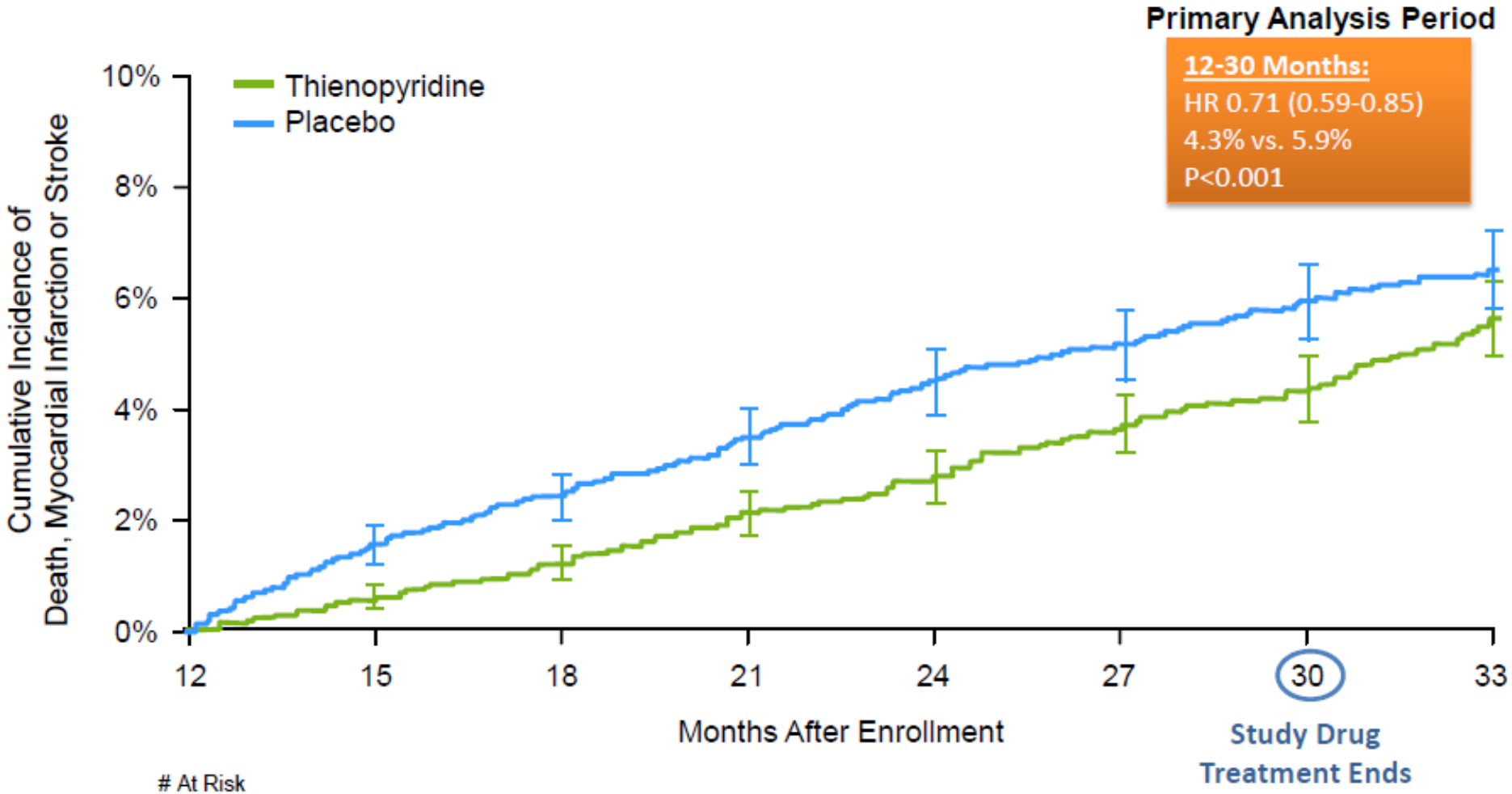
DAPT STUDY



# At Risk								
Thienopyridine	5020	4920	4849	4789	4717	4634	4580	3051
Placebo	4941	4804	4727	4653	4565	4501	4440	3012

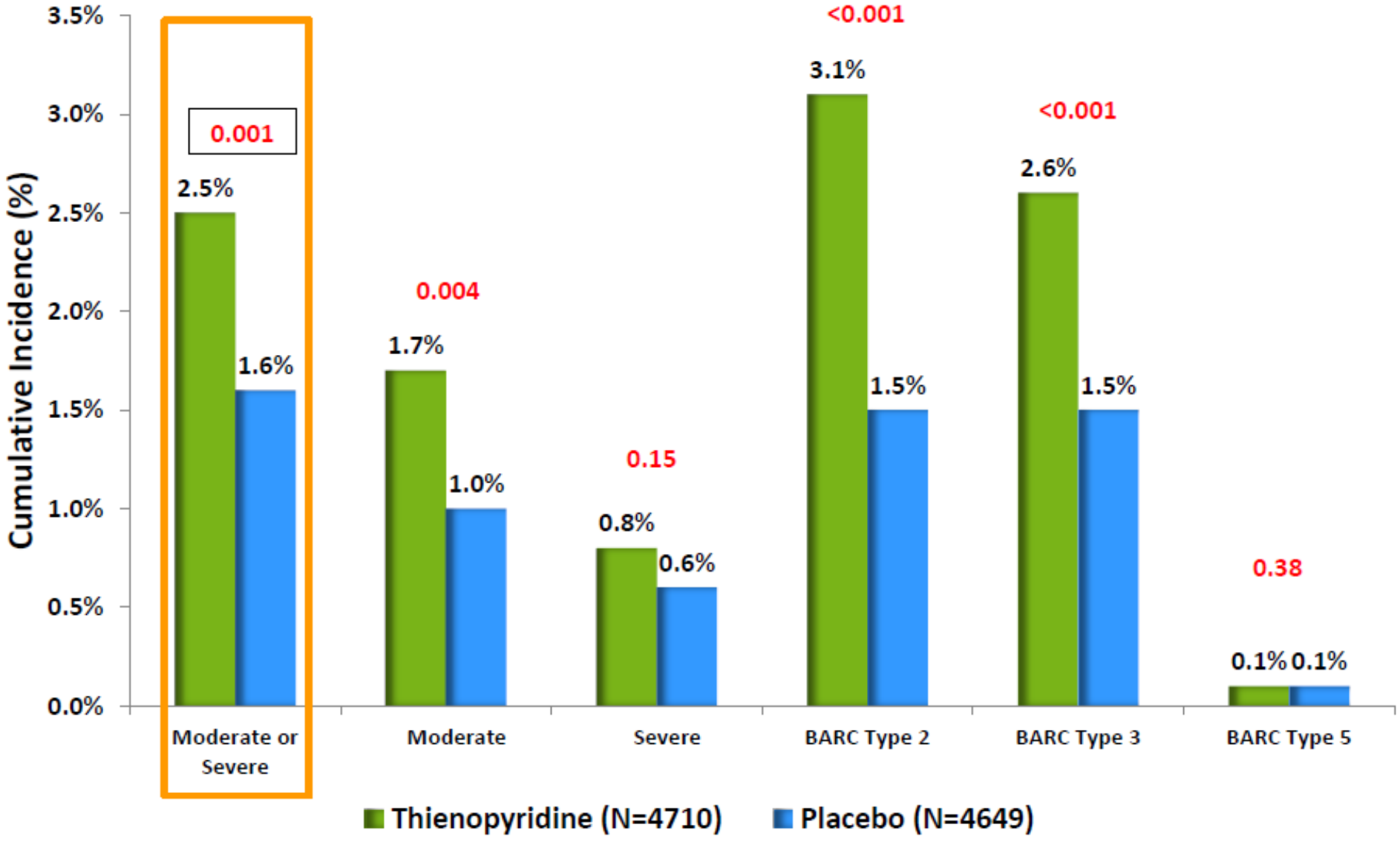
Co-Primary Effectiveness End Point MACCE

DAPT STUDY



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months



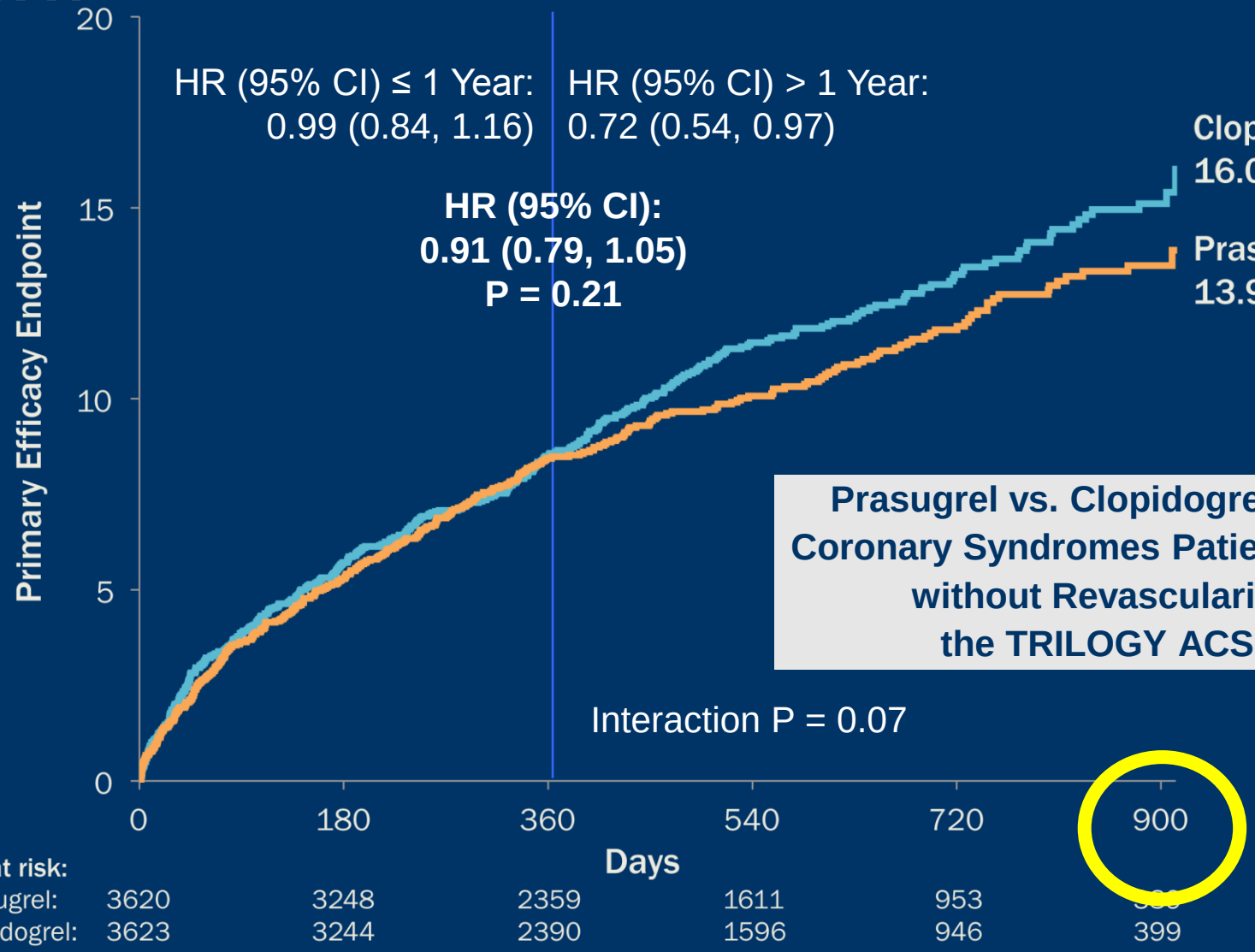
Conclusions

DAPT STUDY

- Following drug-eluting stent treatment, continuation of thienopyridine plus aspirin beyond one year reduces the risk of stent thrombosis and MACCE compared with aspirin alone.
  - Relative reductions of 71% for ST, 29% for MACCE and 53% for M
  - Myocardial infarction reduced both in the stent and in other locations
  - Treatment benefit on ST and MI consistent across drugs, for newer and older stents, and across subjects with higher or lower risk of events
- The benefit of extended thienopyridine treatment was tempered by an increase in bleeding events (relative increase, 61%). Severe and/or fatal bleeding was uncommon.

Primary Efficacy Endpoint to 30 Months

(Age < 75 years)

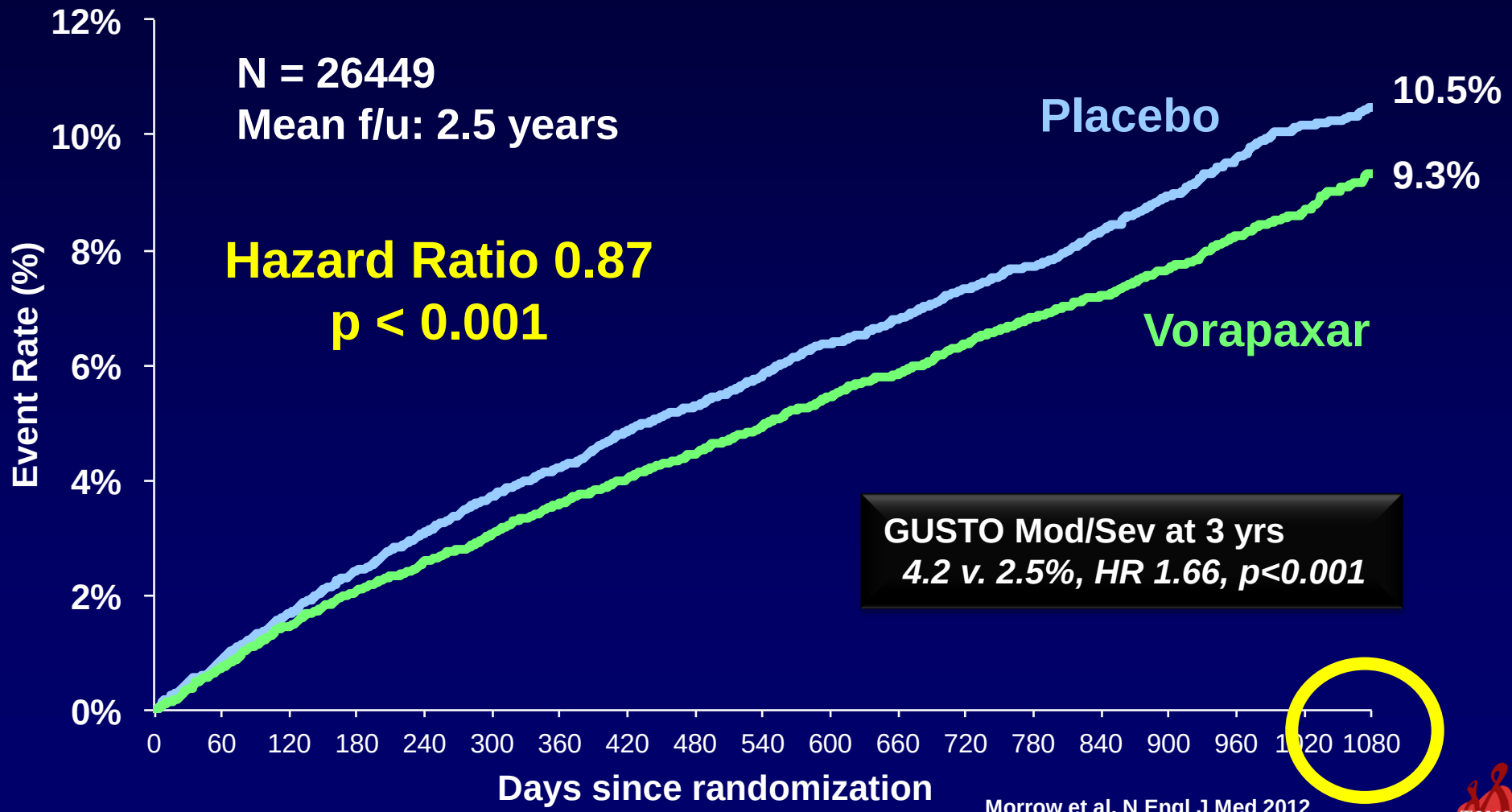


Prasugrel vs. Clopidogrel for Acute Coronary Syndromes Patients Managed without Revascularization the TRILOGY ACS trial

Background – 1° Efficacy Evaluation

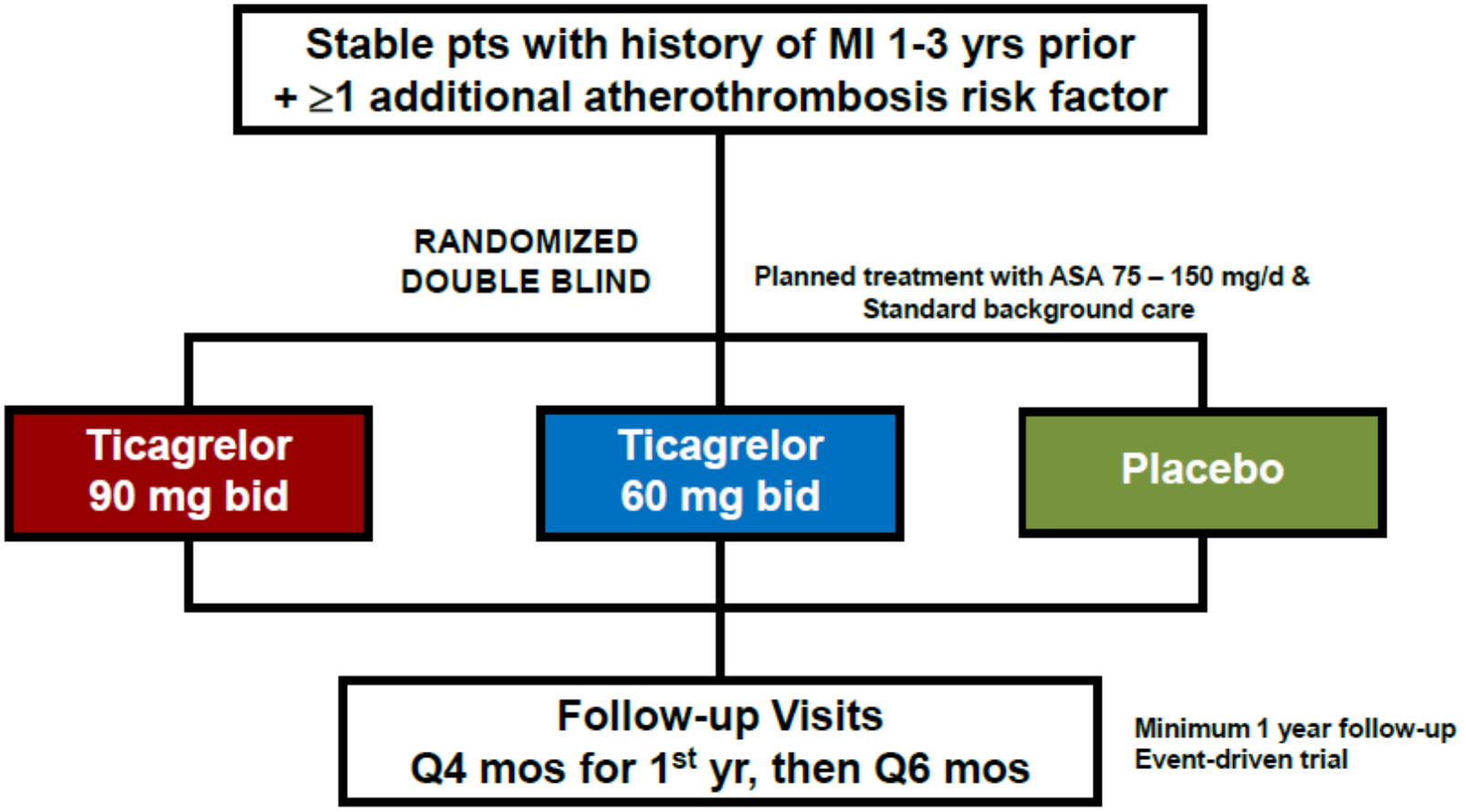
Overall Population

CV Death, MI, or Stroke



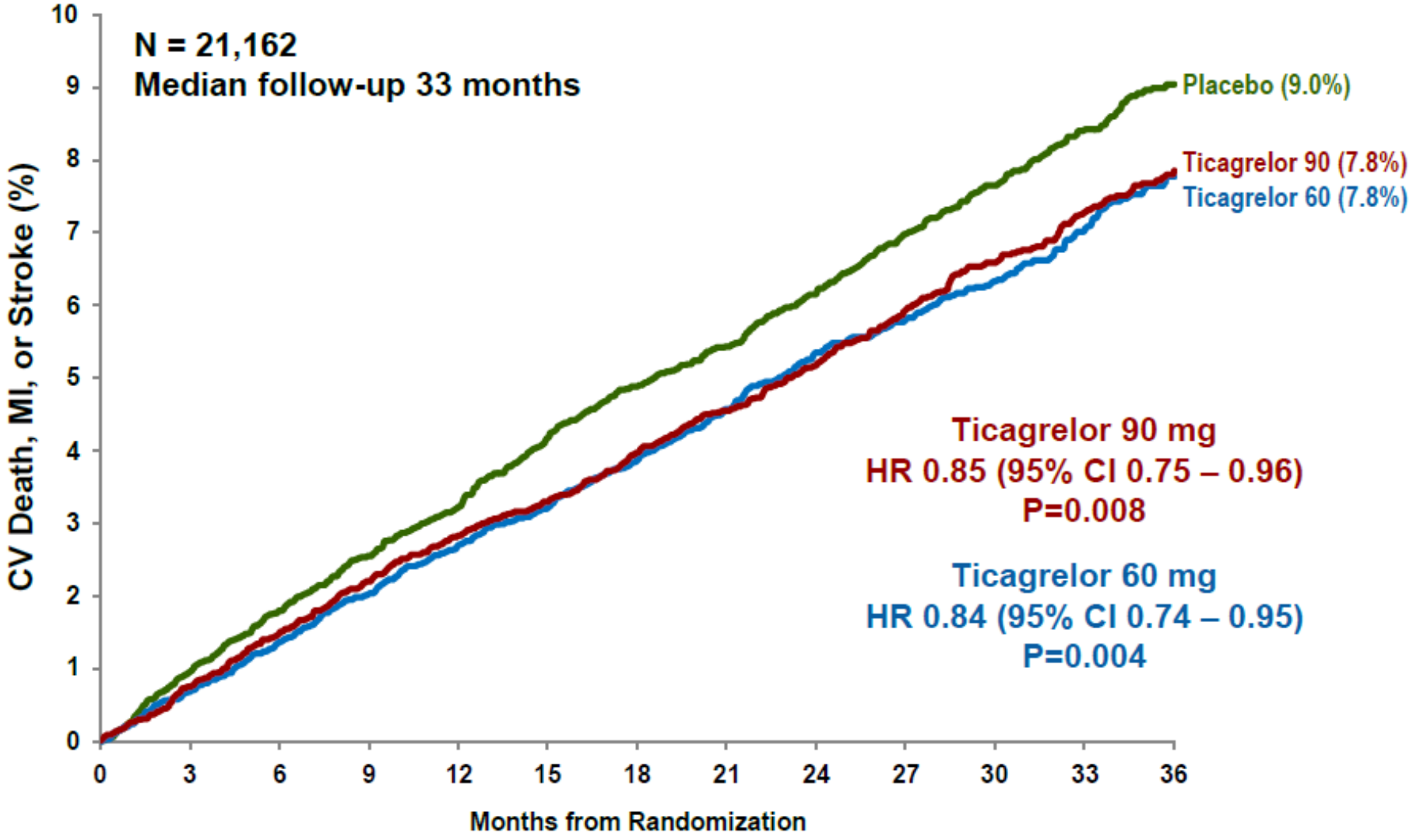
Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474c

Trial Design

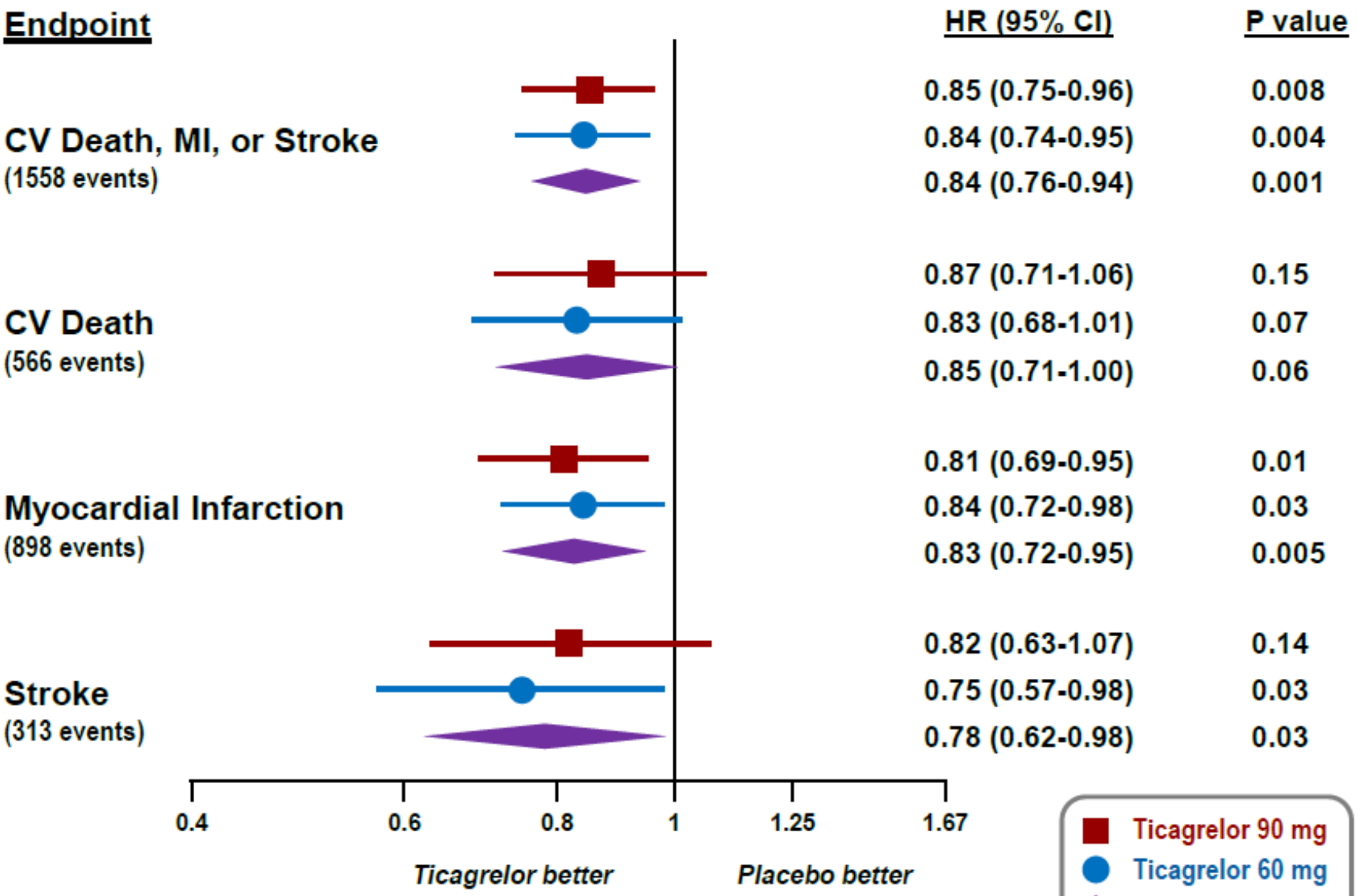


Bonaca MP et al. *Am Heart J* 2014;167:437-44

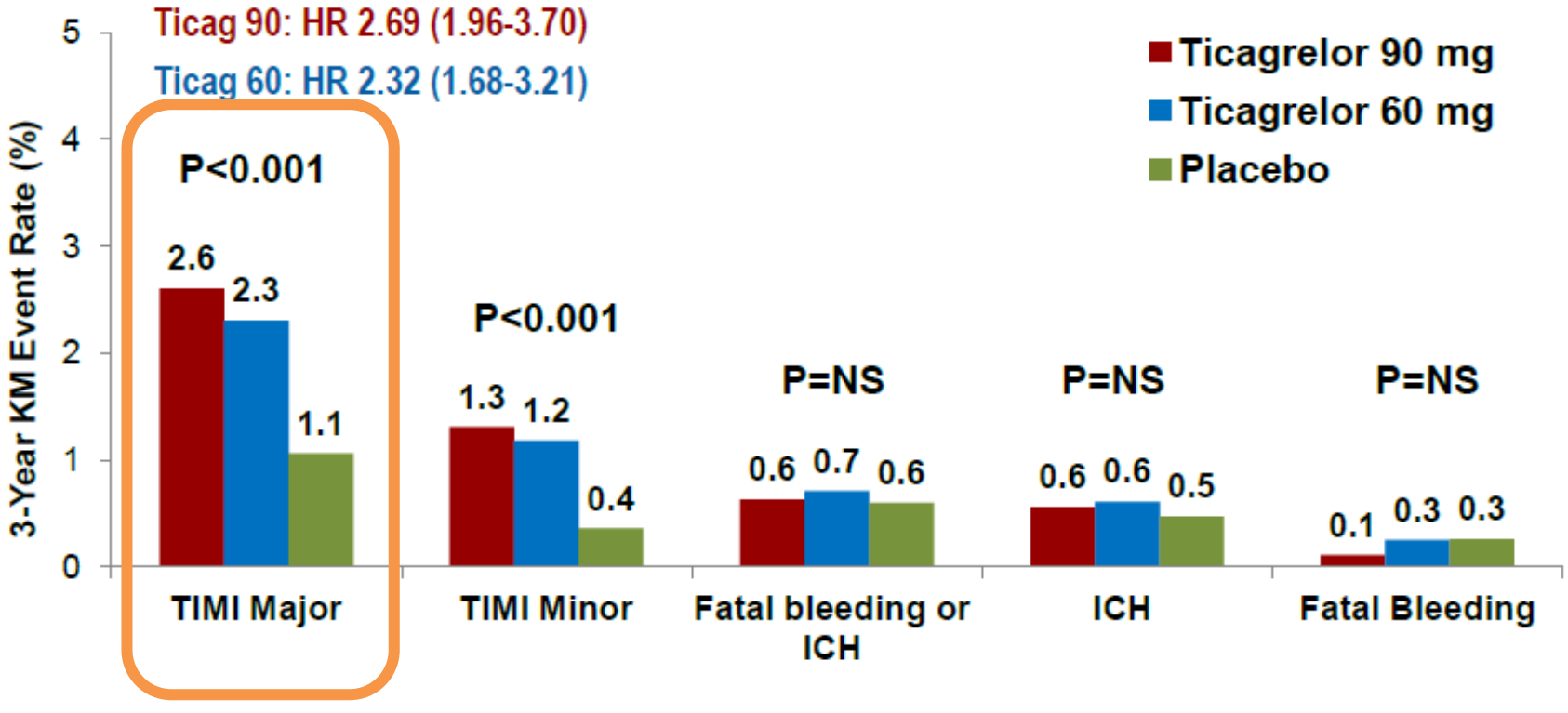
Primary Endpoint



Components of Primary Endpoint

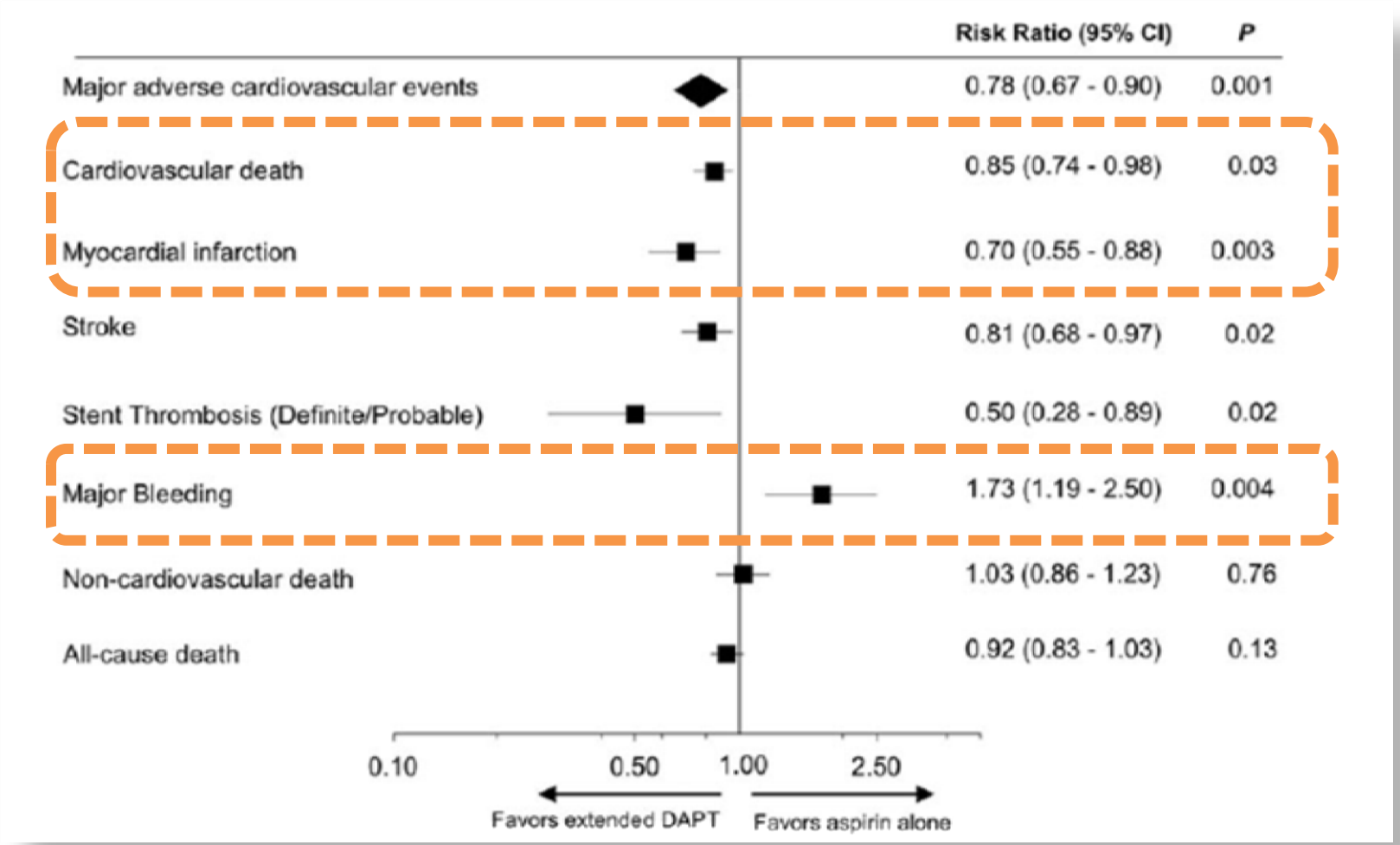


Bleeding


Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

Extended DAPT

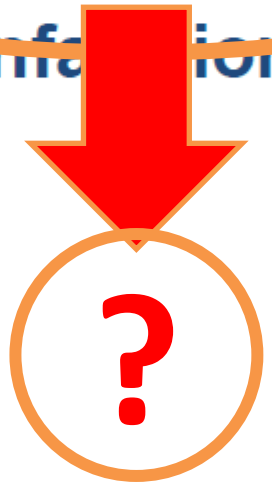
Udell's meta-analysis



European Heart Journal
doi:10.1093/eurheartj/ehv443

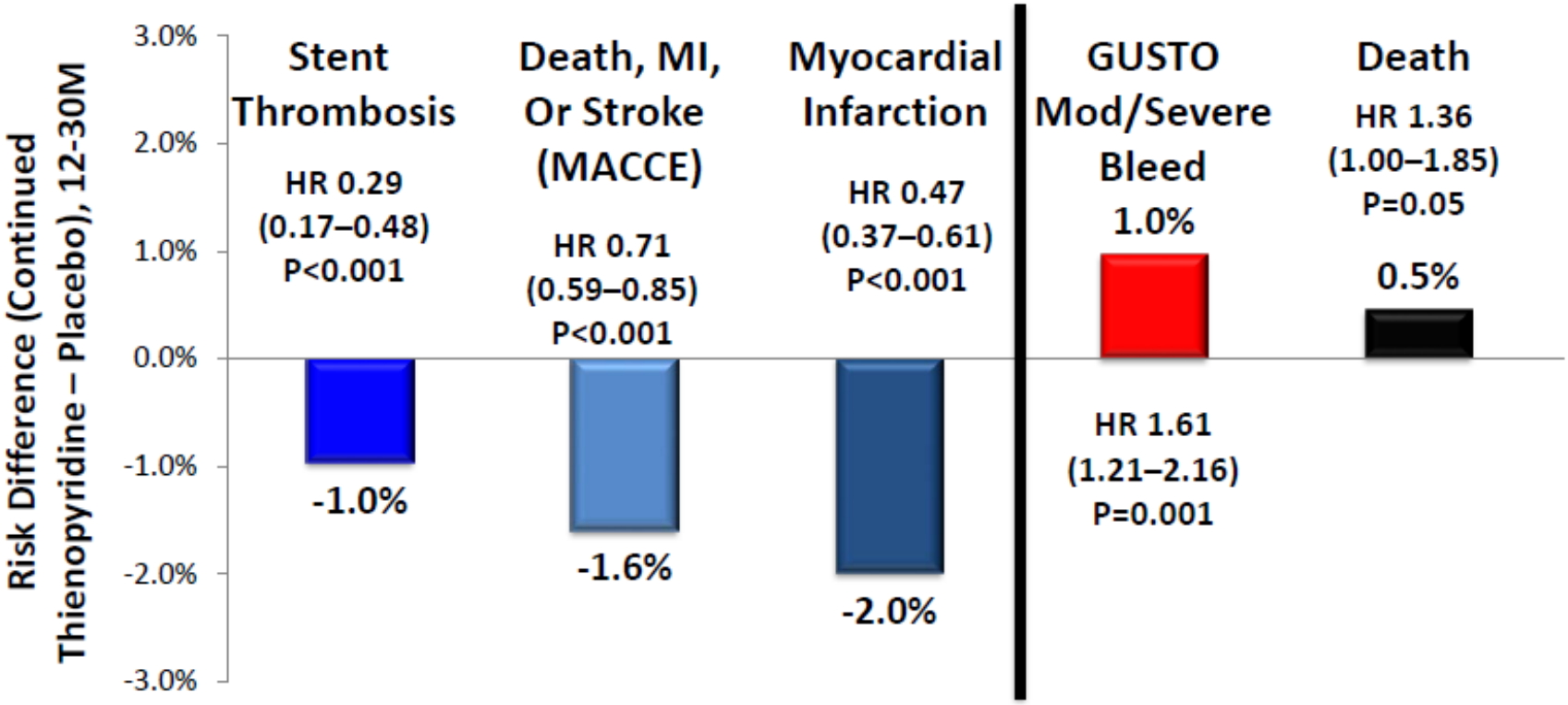
Conclusion

Long-term dual antiplatelet therapy with low-dose aspirin and ticagrelor should be considered in appropriate patients with a myocardial infarction.



Background

- In the DAPT Study, continuation of dual antiplatelet therapy beyond 12 months reduced ischemic complications after coronary stenting compared with aspirin alone, yet increased moderate or severe bleeding.



Mauri, Kereiakes, Yeh et al. NEJM. 2014 Dec 4:371:2155-66.

Multivariable Prediction Models

DAPT STUDY

	Predictors of Myocardial Infarction or Stent Thrombosis		Predictors of Moderate/Severe Bleeding	
Predictors of Events	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Continued Thienopyridine vs. Placebo	0.52 (0.42 – 0.65)	<0.001	1.66 (1.26 - 2.19)	<0.001
MI at Presentation	1.65 (1.31 – 2.07)	<0.001	-	-
Prior PCI or Prior MI	1.79 (1.43 – 2.23)	<0.001	-	-
CHF or LVEF < 30%	1.88 (1.35 – 2.62)	<0.001	-	-
Vein Graft PCI	1.75 (1.13 – 2.73)	0.01	-	-
Stent Diameter < 3 mm	1.61 (1.30 – 1.99)	<0.001	-	-
Paclitaxel-Eluting Stent	1.57 (1.26 – 1.97)	<0.001	-	-
Cigarette Smoker	1.40 (1.11 – 1.76)	0.01	-	-
Diabetes	1.38 (1.10 – 1.72)	0.01	-	-
Peripheral Arterial Disease	1.49 (1.05 – 2.13)	0.03	2.16 (1.46, 3.20)	<0.001
Hypertension	1.37 (1.03 – 1.82)	0.03	1.45 (1.00, 2.11)	0.05
Renal Insufficiency	1.55 (1.03 – 2.32)	0.04	1.66 (1.04, 2.66)	0.03
Age (per 10 years)	-	-	1.54 (1.34, 1.78)	<0.001

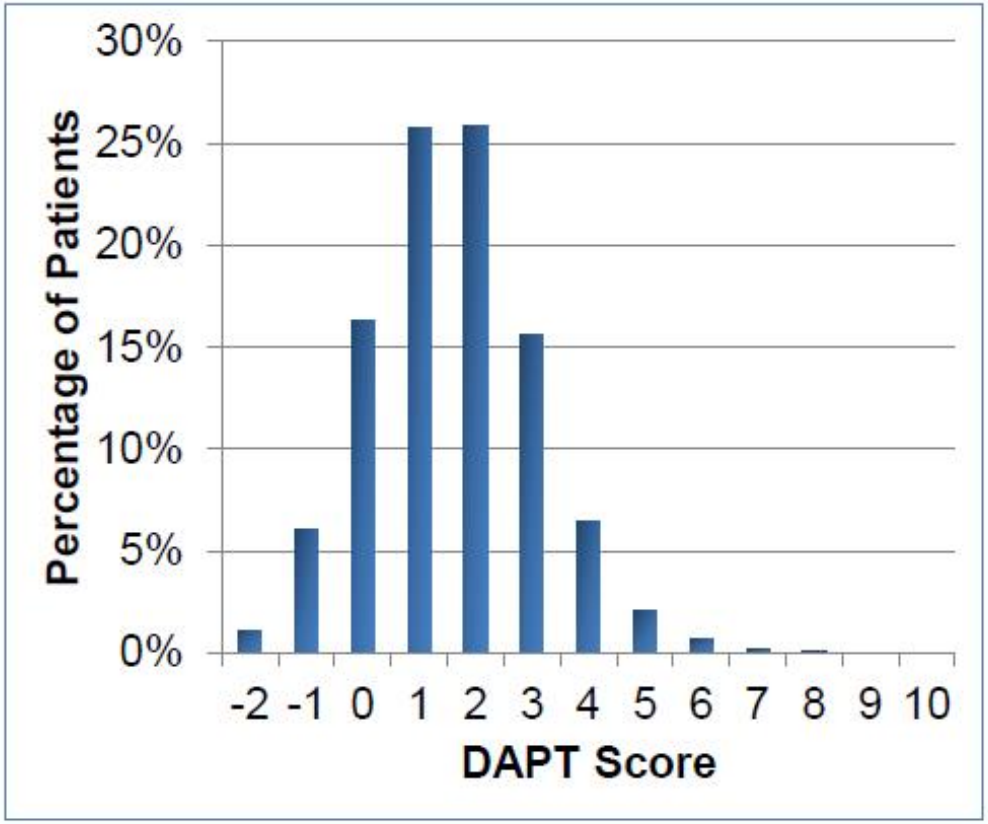
*The ischemia model C-statistic: 0.70 in DAPT Study; 0.64 in PROTECT

**The bleeding model C-statistic: 0.68 in DAPT Study; 0.64 in PROTECT

The DAPT Score

Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

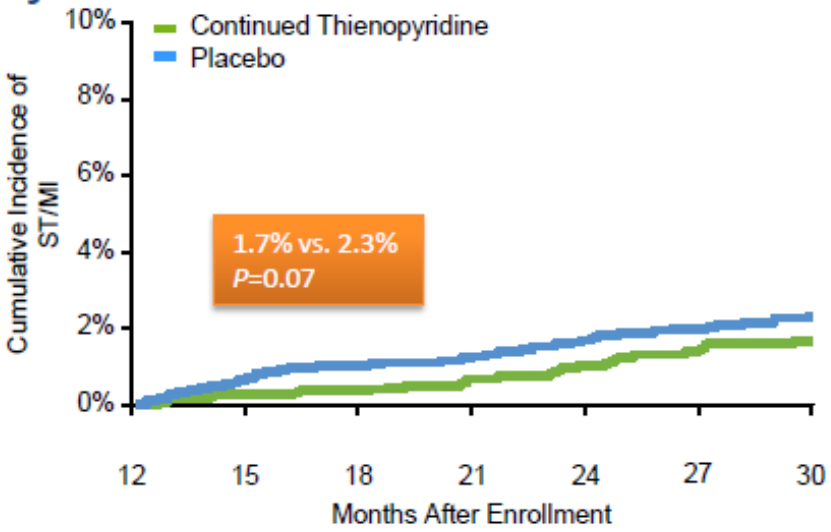
Distribution of DAPT Scores among all randomized subjects in the DAPT Study



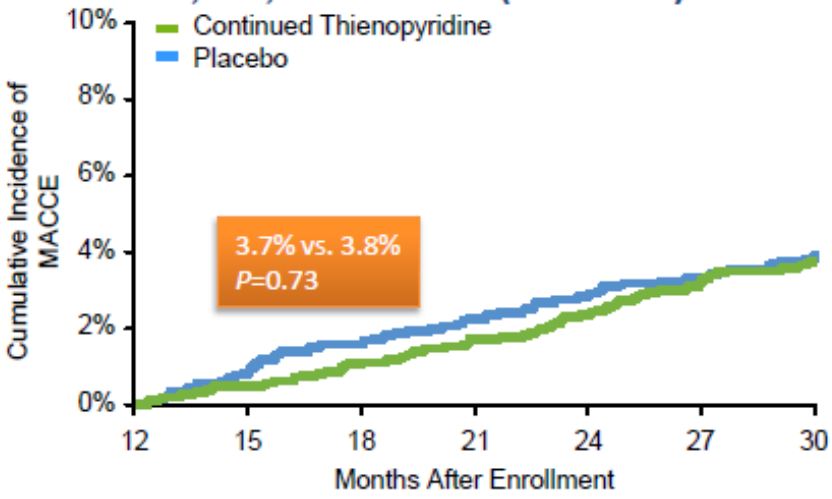
Continued Thienopyridine vs. Placebo
DAPT Score <2 (Low); N=5731

DAPT STUDY

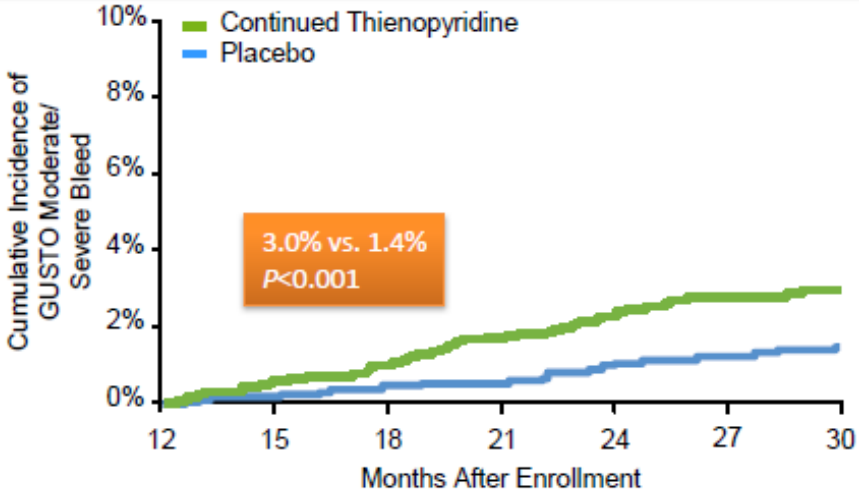
Myocardial Infarction or Stent Thrombosis



Death, MI, or Stroke (MACCE)



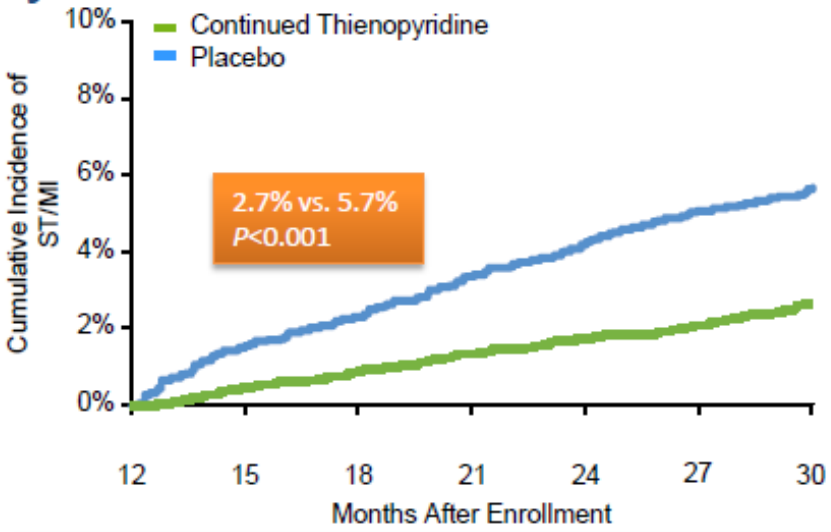
GUSTO Moderate/ Severe Bleeding



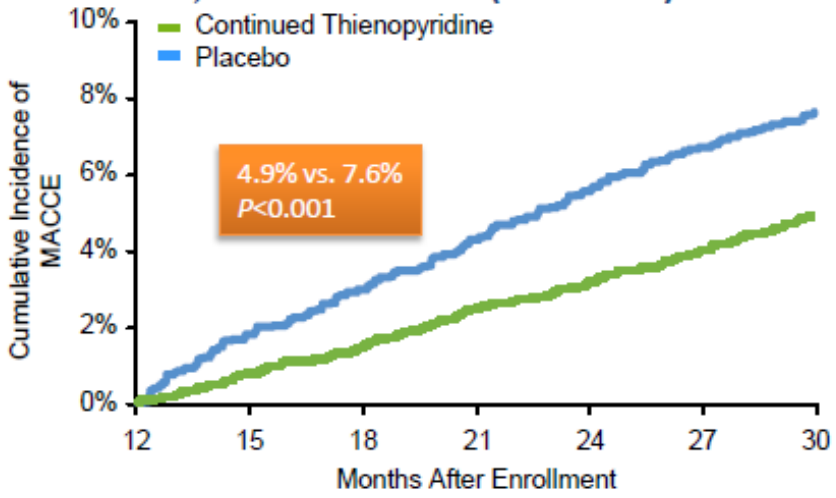
Continued Thienopyridine vs. Placebo
DAPT Score ≥ 2 (High); N=5917

DAPT STUDY

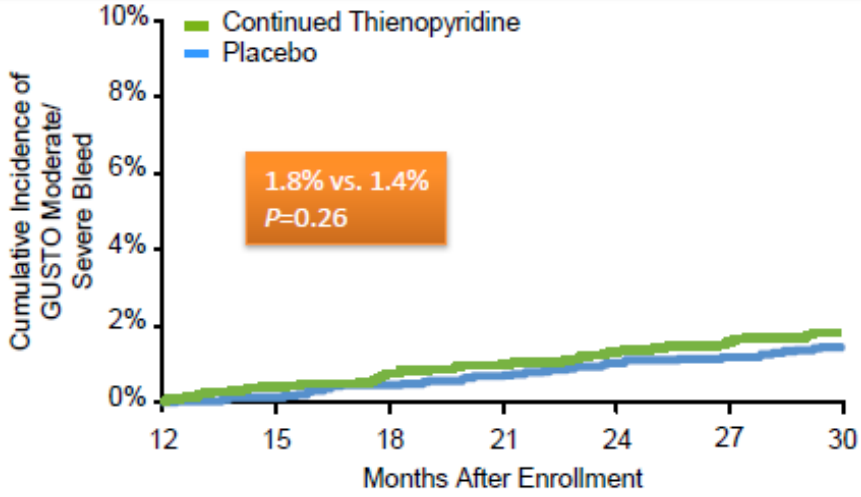
Myocardial Infarction or Stent Thrombosis



Death, MI or Stroke (MACCE)



GUSTO Moderate/ Severe Bleeding



Conclusions

DAPT STUDY

Among patients who have not had a major ischemic or bleeding event within the first year after PCI:

The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, and patients for whom bleeding risks outweighed ischemic benefits.

Low DAPT Score (< 2)
NNT to prevent ischemia = 153
NNH to cause bleeding = 64

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT

Final remarks - I

Patients with an established history of ACS and / or stent implantation may benefit of DAPT prolongation. The exact time duration is unknown

Patient oriented approach should be preferred over a more simplistic way focusing only on the stent

Appropriate patient selection is the key to handle the delicate balance between preventing thrombosis and provoking bleeding

Final remarks - II

Individualized therapy should be based on

Individual characteristics

Thrombotic risk

Bleeding risk

Associated co-factors

DAPT score

Stent characteristics

Type of stent

(nr, length, location, diameter, overlap, dissection)

Coronary anatomy

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Thrombosis
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

Many thanks

João Morais

Head of Cardiology Division
Leiria Hospital Centre
Chairman WG Thrombosis

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